Answer 1:

Bibliographic Information

Proteasome Inhibition Activates Epidermal Growth Factor Receptor (EGFR) and EGFR-Independent Mitogenic Kinase Signaling Pathways in Pancreatic Cancer Cells. Sloss, Callum M.; Wang, Fang; Liu, Rong; Xia, Lijun; Houston, Michael; Ljungman, David; Palladino, Michael A.; Cusack, James C., Jr. Authors' Affiliations: Division of Surgical Oncology, Harvard Medical School, Boston, Massachusetts General Hospital, Massachusetts and Nereus Pharmaceuticals, San Diego, CA, USA. Clinical Cancer Research (2008), 14(16), 5116-5123. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. AN 2008:976367 CAPLUS

Abstract

PURPOSE: In the current study, we investigate the activation of antiapoptotic signaling pathways in response to proteasome inhibitor treatment in pancreatic cancer and evaluate the use of concomitant inhibition of these pathways to augment proteasome inhibitor treatment responses. Exptl. Design: Pancreatic cancer cell lines and mouse flank xenografts were treated with proteasome inhibitor alone or in combination with chemotherapeutic compds. (gemcitabine, erlotinib, and bevacizumab), induction of apoptosis and effects on tumor growth were assessed. The effect of bortezomib (a first-generation proteasome inhibitor) and NPI-0052 (a second-generation proteasome inhibitor) treatment on key pancreatic mitogenic and antiapoptotic pathways [epidermal growth factor receptor, extracellular signal-regulated kinase, and phosphoinositide-3-kinase (PI3K)/AKT] was detd. and the ability of inhibitors of these pathways to enhance the effects of proteasome inhibition was assessed in vitro and in vivo. RESULTS: Our data showed that proteasome inhibitor treatment activates antiapoptotic and mitogenic signaling pathways (epidermal growth factor receptor, extracellular signal-regulated kinase, c-Jun-NH2-kinase, and PI3K/AKT) in pancreatic cancer. Addnl., we found that activation of these pathways impairs tumor response to proteasome inhibitor treatment and inhibition of the c-Jun-NH2-kinase and PI3K/AKT pathways increases the antitumor effects of proteasome inhibitor treatment. CONCLUSION: These preclin. studies suggest that targeting proteasome inhibitor-induced antiapoptotic signaling pathways in combination with proteasome inhibition may augment treatment response in highly resistant solid organ malignancies. Further evaluation of these novel treatment combinations in clin. trials is warranted.

Answer 2:

Bibliographic Information

Anti-apoptotic and growth-stimulatory functions of CK1 delta and epsilon in ductal adenocarcinoma of the pancreas are inhibited by IC261 in vitro and in vivo. Brockschmidt, C.; Hirner, H.; Huber, N.; Eismann, T.; Hillenbrand, A.; Giamas, G.; Radunsky, B.; Ammerpohl, O.; Bohm, B.; Henne-Bruns, D.; Kalthoff, H.; Leithaeuser, F.; Trauzold, A.; Knippschild, U. Clinic of General, Visceral- and Transplantation Surgery, University of Ulm, Germany. Gut (2008), 57(6), 799-806. Publisher: BMJ Publishing Group, CODEN: GUTTAK ISSN: 0017-5749. Journal written in English. CAN 149:119002 AN 2008:751369 CAPLUS

Abstract

Background: Pancreatic ductal adenocarcinomas (PDACs) are highly resistant to treatment due to changes in various signalling pathways. CK1 isoforms play important regulatory roles in these pathways. Aims: We analyzed the expression levels of CK1 delta and epsilon (CK1δ/ε) in pancreatic tumor cells in order to validate the effects of CK1 inhibition by 3-[2,4,6-(trimethoxyphenyl)methylidenyl]-indolin-2-one (IC261) on their proliferation and sensitivity to anti-CD95 and gemcitabine. Methods: CK1δ/ε expression levels were investigated by using western blotting and immunohistochem. Cell death was analyzed by FACS anal. Gene expression was assessed by real-time PCR and western blotting. The putative anti-tumoral effects of IC261 were tested in vivo in a s.c. mouse xenotransplantation model for pancreatic cancer. Results: We found that CK1δ/ε are highly expressed in pancreatic tumor cell lines and in higher graded PDACs. Inhibition of CK1δ/ε by IC261 reduced pancreatic tumor cell growth in vitro and in vivo. Moreover, IC261 decreased the expression levels of several anti-apoptotic proteins and sensitized cells to CD95-mediated apoptosis. However, IC261 did not enhance gemcitabine-mediated cell death either in vitro or in vivo. Conclusions: Targeting CK1 isoforms by IC261 influences both pancreatic tumor cell growth and apoptosis sensitivity in vitro and the growth of induced tumors in vivo, thus providing a promising new strategy for the treatment of pancreatic tumors.

Answer 3:

Bibliographic Information

Experimental therapy of prostate cancer with novel natural product anti-cancer ginsenosides. Wang, Wei; Rayburn, Elizabeth R.; Hao, Miao; Zhao, Yuqing; Hill, Donald L.; Zhang, Ruiwen; Wang, Hui. Department of Pharmacology and Toxicology and Division of Clinical Pharmacology, and Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL, USA. Prostate (Hoboken, NJ, United States) (2008), 68(8), 809-819. Publisher: Wiley-Liss, Inc., CODEN: PRSTDS ISSN: 0270-4137. Journal written in English. AN 2008:746746 CAPLUS

Abstract

BACKGROUND: Ginseng and its components exert various biol. effects, including antioxidant, anti-carcinogenic, anti-mutagenic, and anti-tumor activity, and recent research has focused on their value in human cancer prevention and treatment. We recently isolated 25-hydroxyprotopanaxadiol (25-OH-PPD) and 25-hydroxyprotopanaxatriol (25-OH-PPT) from Panax ginseng and evaluated their anti-cancer activity in vitro. METHODS: We compared the effects of the two compds. on human prostate cancer LNCaP and PC3 cells in vitro and in a mouse PC3 xenograft tumor model. We also accomplished a preliminary detn. of the mechanisms of action of the compds. RESULTS: 25-OH-PPD, but not 25-OH-PPT, inhibited prostate cancer cell growth and proliferation, induced apoptosis, and led to arrest in the G1 phase of the cell cycle. In nude mice bearing PC3 xenograft tumors, 25-OH-PPD inhibited tumor growth in a dose-dependent manner and could be safely combined with chemotherapeutic agents (taxotere and gemcitabine) and radiation therapy to improve the anti-tumor effects. Further, in both PC3 and LNCaP cell lines, 25-OH-PPD increased expression of p21, p27, and Bax, induced PARP cleavage and activated caspases. The compd. also reduced expression of MDM2, E2F1, Bcl2, cdk2/4/6, and cyclin D1, which correlated with the cell cycle arrest in G1 and the decrease in proliferation. Moreover, 25-OH-PPD demonstrated low toxicity to non-cancer cells and no observable host toxicity in animals either alone or in combination with conventional therapies. CONCLUSIONS: The newly identified ginsenoside 25-OH-PPD may have potential as a novel prostate cancer therapeutic agent.

Answer 4:

Bibliographic Information

Epidermal Growth Factor Receptor Blockade in Combination with Conventional Chemotherapy Inhibits Soft Tissue Sarcoma Cell Growth In vitro and In vivo. Ren, Wenhong; Korchin, Borys; Zhu, Quan-Sheng; Wei, Caimiao; Dicker, Adam; Heymach, John; Lazar, Alexander; Pollock, Raphael E.; Lev, Dina. Departments of Surgical Oncology, Cancer Biology, Medical Oncology, and Pathology and Division of Quantitative Sciences, University of Texas, M. D. Anderson Cancer Center, Houston, TX, USA. Clinical Cancer Research (2008), 14(9), 2785-2795. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 149:191182 AN 2008:549995 CAPLUS

Abstract

PURPOSE: The epidermal growth factor receptor (EGFR) is highly expressed in many human soft tissue sarcomas (STS). However, EGFR blockade has not apparently been used for human STS therapy; therefore, we examd. the in vitro and in vivo effects and the underlying mechanisms before considering EGFR blockade as a therapy for STS patients. Exptl. Design: Human STS tissues and cell lines were used to study EGFR expression and activation. Western blot anal. was used to evaluate effects of EGFR activation on downstream signaling. Cell culture assays were used to assess the effect of EGF stimulation as well as EGFR blockade (using an EGFR tyrosine kinase inhibitor, Iressa; AstraZeneca) on STS cell growth, apoptosis, and chemosensitivity. An in vivo study (HT1080 human fibrosarcoma cell line in nude/nude mice: Iressa, doxorubicin, Iressa + doxorubicin, vehicle) was used to examine tumor growth; pEGFR, proliferating cell nuclear antigen, and terminal deoxyribonucleotide transferase-mediated nick-end labeling staining helped assess the effect of therapy in vivo on STS EGFR activation, proliferation, and apoptosis. RESULTS: EGFR was expressed and activated in STS cell lines and tumors, probably due to ligand binding rather than EGFR mutation. Stimulation caused activation of AKT and mitogen-activated protein kinase pathways. EGFR blockade inhibited these effects and also caused increased apoptosis, a p53-independent G0-G1 cell cycle arrest, and decreased cyclin D1 expression. In vivo, Iressa + doxorubicin had markedly synergistic anti-STS effects. CONCLUSION: EGFR blockade combined with conventional chemotherapy results in anti-human STS activity in

vitro and in vivo, suggesting the possibility that combining these synergistic treatments will improve anti-STS therapy.

Answer 5:

Bibliographic Information

HMGA1 Is a Molecular Determinant of Chemoresistance to Gemcitabine in Pancreatic Adenocarcinoma. Liau, Siong-Seng; Whang, Edward. Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. Clinical Cancer Research (2008), 14(5), 1470-1477. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. AN 2008:270829 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: HMGA1 proteins are architectural transcription factors that are overexpressed by pancreatic adenocarcinomas. We previously have shown that RNA interference targeting the HMGA1 gene may represent a potential chemosensitizing strategy in pancreatic adenocarcinoma cells. In this study, we tested the hypothesis that HMGA1 promotes chemoresistance to gemcitabine in pancreatic cancer cells. Exptl. Design and Results: Stable short hairpin RNA-mediated HMGA1 silencing in BxPC3 and MiaPaCa2 cells promoted chemosensitivity to gemcitabine, with redns. in gemcitabine IC50 and increases in gemcitabine-induced apoptosis and caspase-3 activation. In contrast, forced HMGA1 overexpression in MiaPaCa2 cells promoted chemoresistance to gemcitabine, with increases in gemcitabine IC50 and redns. in gemcitabine-induced apoptosis and caspase-3 activation. Dominant neg. Akt abrogated HMGA1 overexpression-induced increases in chemoresistance to gemcitabine. Finally, HMGA1 silencing promoted chemosensitivity to gemcitabine in vivo in a nude mouse xenograft model of pancreatic adenocarcinoma. CONCLUSION: Our findings suggest that HMGA1 promotes chemoresistance to gemcitabine through an Akt-dependent mechanism. Targeted therapies directed at HMGA1 represent a potential strategy for ameliorating chemoresistance in pancreatic adenocarcinoma.

Answer 6:

Bibliographic Information

Gemcitabine Resistance in Pancreatic Cancer: Picking the Key Players. Kim, Michael P.; Gallick, Gary E. Department of Cancer Biology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA. Clinical Cancer Research (2008), 14(5), 1284-1285. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal; General Review written in English. CAN 149:61 AN 2008:270797 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. The research of Liau et al. (2008) entitled "HMGA1 is a mol. determinant of chemoresistance to gemcitabine in pancreatic adenocarcinoma" is reviewed with commentary and refs. The authors focused on the effect of gemcitabine treatment on HMGA1 knockdown cells. They found that gemcitabine administration in mice bearing s.c. xenografts of BXPC3 cells, in which HMGA1 was down-regulated, led to tumor regression. Identification of gene products that affect gemcitabine resistance, such as HMGA1, is a fundamental step in understanding the key mol. players that promote the acquisition of deadly cancer phenotypes. Their study implicates that it is feasible to identify "gemcitabine-sensitizing agents"-drugs that attenuate inherent and acquired resistance to gemcitabine.

Answer 7:

Bibliographic Information

Effect of Z-360, a novel orally active CCK-2/gastrin receptor antagonist on tumor growth in human pancreatic adenocarcinoma cell lines in vivo and mode of action determinations in vitro. Kawasaki, Daisuke; Emori, Yutaka; Eta, Runa; Iino, Yuka; Hamano, Hiroki; Yoshinaga, Koji; Tanaka, Takao; Takei, Mineo; Watson, Susan A. Central Research Laboratories, Zeria

Pharmaceutical Co., Ltd, Kumagaya-City, 2512-1, Numagami, Oshikiri, Japan. Cancer Chemotherapy and Pharmacology (2008), 61(5), 883-892. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 148:576053 AN 2008:233900 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose Gastrin is known to enhance the growth of pancreatic carcinoma via the cholecystokinin (CCK)-2/gastrin receptor. We investigated the anti-tumor effect of Z-360 (calcium bis [(R)-(-)-3-[3-{5-cyclohexyl-1-(3,3-dimethyl-2-oxo-butyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl}ureido]benzoate]), a novel orally active CCK-2 receptor antagonist alone or combined with the chemotherapeutic agent, gemcitabine in human pancreatic adenocarcinoma cell lines. Results Z-360 potently inhibited specific binding of [3H]CCK-8 to the human CCK-2 receptor, with a Ki value of 0.47 nmol/l, and showed antagonistic activity for this receptor. The anti-tumor effect of Z-360 alone or combined with gemcitabine was assessed using s.c. xenografts of MiaPaCa2 and PANC-1 and an orthotopic xenograft model (PANC-1). Oral administration of Z-360 significantly inhibited the growth of MiaPaCa2 (41.7% inhibition at 100 mg/kg, $P < 0.01$). Combined administration of Z-360 and gemcitabine significantly inhibited s.c. PANC-1 tumor growth compared with either agent alone (27.1% inhibition compared to effect with gemcitabine, $P < 0.05$), and significantly prolonged survival compared with the vehicle control (median survival of 49 days in vehicle compared to 57 days in the combination group, $P < 0.05$). In vitro studies showed that Z-360 significantly inhibited gastrin-induced proliferation of human CCK-2 receptor-expressing cells, and also significantly reduced gastrin-induced PKB/Akt phosphorylation to the level of untreated controls. Conclusion In the present study, we have shown that Z-360 combined with gemcitabine can inhibit pancreatic tumor growth and prolong survival in a pancreatic carcinoma xenograft model, on a possible mode of action being the inhibition of gastrin-induced PKB/Akt phosphorylation through blockade of the CCK-2 receptor. Our results suggest that Z-360 may be a useful adjunct to gemcitabine for the treatment of pancreatic carcinoma and a therapeutic option for patients with advanced pancreatic cancer.

Answer 8:

Bibliographic Information

Cytidine triphosphate synthetase (CTP synthetase) as a druggable target in cancer. Verschuur, Arnauld C. Pediatric Oncology Department, Emma Children's Hospital, University of Amsterdam, Amsterdam, Neth. Drugs of the Future (2007), 32(12), 1071-1080. Publisher: Prous Science, CODEN: DRFUD4 ISSN: 0377-8282. Journal; General Review written in English. CAN 148:393577 AN 2008:216937 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. Cytidine triphosphate (CTP) synthetase is a key enzyme in the biosynthesis of pyrimidine ribonucleotides. The enzyme catalyzes the conversion of uridine triphosphate (UTP) to CTP and is the predominant pathway for the synthesis of CTP in proliferating and malignant tissues. Elevated CTP synthetase activity is seen in various malignancies, such as acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), hepatoma, colon cancer and renal carcinoma, as well as non-Hodgkin's lymphoma (NHL). The high activity of the enzyme has led to the development of inhibitors as potential new therapeutic tools. The best explored inhibitor of CTP synthetase is cyclopentenyl cytosine (CPEC), which has been investigated in both preclin. and clin. studies. CPEC proved to profoundly inhibit CTP synthetase in vitro in colon carcinoma, ALL and AML cell lines. Moreover, CPEC has been shown to inhibit the growth of human and murine leukemia xenografts in vivo. A phase I clin. trial with CPEC as monotherapy showed that this compd. inhibits CTP synthetase in surrogate tissues such as bone marrow. However, at the highest doses, CPEC proved to have severe cardiovascular toxicity, the mechanism of which has not been unraveled until recently. Addnl. preclin. studies did not show any cardiotoxicity in rats. There is probably a good rationale for using CPEC at lower doses, since it has been shown in preclin. models to display synergistic cytotoxic effects with other nucleoside analogs such as cytarabine or gemcitabine. In conclusion, CTP synthetase is a druggable target, esp. for combination treatment of AML and ALL.

Answer 9:

Bibliographic Information

Imatinib Mesylate Enhances Therapeutic Effects of Gemcitabine in Human Malignant Mesothelioma Xenografts. Bertino, Pietro; Piccardi, Federica; Porta, Camillo; Favoni, Roberto; Cilli, Michele; Mutti, Luciano; Gaudino, Giovanni. Department of Chemical, Food, Pharmaceutical and Pharmacological Sciences and Drug and Food Biotechnology Center, University of Piemonte Orientale A. Avogadro, Novara, Italy. Clinical Cancer Research (2008), 14(2), 541-548. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 149:118850 AN 2008:106226 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: Platelet-derived growth factor receptor β (PDGFRβ), frequently activated in malignant mesothelioma, is a promising cancer therapeutic target. Imatinib mesylate (STI571; Glivec) is a selective inhibitor of tyrosine kinases as bcr-abl, c-kit, c-fms, and PDGFRβ and enhances tumor drug uptake by reducing the interstitial fluid pressure. We previously showed that imatinib mesylate synergizes with gemcitabine and pemetrexed in PDGFRβ-pos. mesothelioma cells. Here, we aimed at investigating these combined treatments in a novel mesothelioma model. Exptl. Design: REN mesothelioma cells, infected with a lentiviral vector carrying the luciferase gene, were injected in the peritoneum of severe combined immunodeficient mice. This model allowed imaging of live animals treated with pemetrexed or gemcitabine chemotherapeutics, or with imatinib mesylate alone, as well as with a combination of gemcitabine and imatinib mesylate. RESULTS: We show here that, consistent with our previous in vitro studies, gemcitabine inhibited tumor growth, whereas pemetrexed was ineffective, even at the highest dosage tested. Compared with monotreatment, the combination of gemcitabine with imatinib mesylate led to a further tumor growth inhibition and improved mice survival, by a decrease rate of tumor cell proliferation and an increase in no. of apoptotic tumor cells. CONCLUSIONS: Imatinib mesylate enhances the therapeutic response to gemcitabine, in accordance with our previous in vitro data. These in vivo results validate imatinib mesylate and gemcitabine as a combination treatment of malignant mesothelioma, also in view of its known pos. effects on tumor drug uptake. These evidences provide the rationale for the currently ongoing clin. trials.

Answer 10:

Bibliographic Information

Impact of imatinib* on the pharmacokinetics and in vivo efficacy of etoposide and/or ifosfamide. Rezai, Keyvan; Lokiec, Francois; Grandjean, Isabelle; Weill, Sophie; de Cremoux, Patricia; Bordier, Vincent; Ekue, Richard; Garcia, Mickael; Poupon, Marie-France; Decaudin, Didier. Department of Pharmacology Oncology, Centre Rene Huguenin, Saint-Cloud, Fr. BMC Pharmacology (2007), 7 No pp. given. Publisher: BioMed Central Ltd., CODEN: BPMHBU ISSN: 1471-2210. http://www.biomedcentral.com/content/pdf/1471-2210-7-13.pdf Journal; Online Computer File written in English. CAN 148:229420 AN 2008:77247 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Using a human small cell lung cancer (SCLC) xenografted in nude mice, we have previously reported enhanced tumor growth inhibition following chemotherapy in combination with imatinib (STI571). We therefore investigated the in vivo impact of imatinib on the pharmacokinetics and efficacy of chemotherapy. Methods: Two different human tumors were used: SCLC6 small cell lung cancer xenografted in nude mice, and LY-3 EBV-assocd. human B-cell lymphoma xenografted in SCID mice. Plasma, urine, and fecal concns. of etoposide (VP16) were detd. by a validated high performance liq. chromatog. method. Plasma concns. of ifosfamide were detd. by a validated gas chromatog. assay with nitrogen-phosphorus detection. Results: Slight tumor growth inhibition was induced by imatinib administered alone in one in vivo EBV-assocd. B-cell lymphomatous xenograft. In contrast, an increase of the chemotherapy-induced antitumor effect was obsd. in the lymphoma model but not in a small cell lung cancer model when mice bearing human xenografted tumors were treated concomitantly by imatinib and chemotherapy. This antitumor effect was not influenced by concomitant administration of fluconazole. The AUC0-3h (Area Under the concn.-time Curve) of etoposide was increased when mice were treated with etoposide + imatinib due to decreased fecal excretion. In contrast, imatinib did not appear to influence the urinary excretion of etoposide, and concomitant administration of the CYP3A4 inhibitor, fluconazole, with imatinib did not modify the pharmacokinetics of etoposide plus imatinib alone. Conclusions: Altogether, these results therefore justify further prospective phase I and II clin. trials with combinations of etoposide-based chemotherapy and imatinib in patients with certain cancers, such as malignant lymphoma, with careful toxicol. monitoring.

Answer 11:

Bibliographic Information

Superiority of extended neoadjuvant chemotherapy with gemcitabine in pancreatic cancer: a comparative analysis in a clinically adapted orthotopic xenotransplantation model in SCID beige mice. Egberts, Jan-Hendrik; Schniewind, Bodo; Sipos, Bence; Hinz, Sebastian; Kalthoff, Holger; Tepel, Juergen. Department of General Surgery and Thoracic Surgery, University Hospital of Schleswig-Holstein, Kiel, Germany. Cancer Biology & Therapy (2007), 6(8), 1227-1232. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 148:417403 AN 2008:48217 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Intensive efforts are being made to develop new approaches for adjuvant or neoadjuvant treatment in pancreas carcinoma. Recently, we established an animal model simulating an adjuvant therapeutic treatment setting. In order to addnl. mimic a neoadjuvant treatment regime, we further developed the preclin. testing system. Methods: Subtotal pancreatectomy was performed in mice after orthotopic inoculation of human pancreatic cancer cells (PancTu1). Four different settings were investigated: control without chemotherapy, adjuvant, neoadjuvant and extended neoadjuvant treatment protocols employing gemcitabine. All animals were autopsied 28 days after tumor resection. Results: 28 of 32 animals survived the treatment setting. The largest pancreatic tumor masses were seen in animals without any chemotherapy, and the different chemotherapy protocols resulted in a stepwise redn. of the tumor mass. The mean wt. of locally recurrent tumors was 553.1 ± 133.2 mg (control) and 44 ± 21.8 mg (adjuvant treatment group). Animals in the neoadjuvant treatment group developed larger tumor masses (215 ± 191.3 mg) but fewer organ metastases. An extended neoadjuvant treatment setting proved to be most effective, resulting in the smallest tumor masses (25.6 ± 8.8 mg) and the fewest organ metastases. Conclusion: Murine orthotopic tumor resection is an excellent simulation of the clin. situation and therefore provides a relevant option for preclin. comparative testing of new therapeutic strategies. To our knowledge, this is the first model described, in which all different therapeutic regimes for pancreatic carcinoma were systematically compared with each other in a standardized manner. The extended neoadjuvant regime proved to be superior.

Answer 12:

Bibliographic Information

Anti-Mesothelin Immunotoxin SS1P in Combination with Gemcitabine Results in Increased Activity against Mesothelin-Expressing Tumor Xenografts. Hassan, Raffit; Broaddus, V. Courtney; Wilson, Shannon; Liewehr, David J.; Zhang, Jingli. Laboratory of Molecular Biology, National Cancer Institute, NIH, Bethesda, MD, USA. Clinical Cancer Research (2007), 13(23), 7166-7171. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 148:486473 AN 2007:1381648 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: To det. the antitumor activity of the anti-mesothelin immunotoxin SS1P in combination with gemcitabine against mesothelin-expressing tumor xenografts. Exptl. Design: The in vitro activity of SS1P in combination with gemcitabine against the mesothelin-expressing cell line A431/K5 was evaluated using cytotoxicity and apoptosis assays. The antitumor activity of this combination was evaluated in nude mice bearing A431/K5 tumor xenografts. Tumor-bearing mice were treated with different doses and schedules of gemcitabine alone, SS1P alone (0.2 mg/kg i.v. every other day x three doses), or with both agents together, and tumor vols. were measured over time. Results: In vitro studies failed to show the synergy of SS1P plus gemcitabine against the mesothelin-expressing A431/K5 cells. In contrast, in the in vivo setting, there was a marked synergy when SS1P was combined with gemcitabine for the treatment of mesothelin-expressing tumor xenografts. This synergy was present using different doses and schedules of gemcitabine administration. In mice treated with fractionated doses of gemcitabine in combination with SS1P, complete tumor regression was obsd. in all mice and was long-lasting in 60% of the animals. Also, this antitumor activity was specific to SS1P because HA22, an immunotoxin targeting CD22 not expressed on A431/K5 cells, did not increase the efficacy of gemcitabine. Conclusions: SS1P in combination with gemcitabine results in marked antitumor activity against mesothelin-expressing tumors. This combination could be potentially useful for the treatment of human cancers that express mesothelin and are responsive to gemcitabine

therapy.

Answer 13:

Bibliographic Information

Orally administered FTS (salirasib) inhibits human pancreatic tumor growth in nude mice. Haklai, Roni; Elad-Sfadia, Galit; Egozi, Yaakov; Kloog, Yoel. Department of Neurobiochemistry, George S. Wise Faculty of Life Sciences, Tel Aviv University, Tel Aviv-Jaffa, Israel. Cancer Chemotherapy and Pharmacology (2007), Volume Date 2008, 61(1), 89-96. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 148:205540 AN 2007:1108791 CAPLUS

Abstract

S-trans,trans-farnesylthiosalicylic acid (salirasib, FTS) is a synthetic small mol. that acts as a potent Ras inhibitor. Salirasib inhibits specifically both oncogenically activated Ras and growth factor receptor-mediated Ras activation, resulting in the inhibition of Ras-dependent tumor growth. The objectives of this study were to develop a sensitive LC-MS/MS assay for detn. of FTS in plasma, to assess the bioavailability of FTS after oral administration to mice, and then to examine the efficacy of orally administered FTS for inhibition of tumor growth in a nude mouse model. FTS was isolated from mouse plasma by liq. chromatog. on a Columbus 5-μm particle size, 50 × 2 mm id column with a methanol/5 mM ammonium acetate (80/20) mobile phase (isocratic elution) at a flow rate of 0.3 mL/min. MS/MS was performed on a PE Sciex API 365 with Turbo Ion Spray as interface and neg. ion ionization; parent ion (m/z): 357.2; daughter ion (m/z) 153.2; retention time 2.3 min. For plasma anal., the amt. of analyte in each sample was calcd. by comparing response of the analyte in that sample to a nine-point std. curve linear over the range 3-1000 ng/mL. Pharmacokinetic studies were performed in mice following i.p. dosing (20 mk/kg in PBS) or oral dosing (40 mg/kg in either 0.5% aq. CMC or corn oil). Panc-1 tumor growth in nude mice was detd. following daily oral dosing with FTS in 0.5% CMC (40, 60, or 80 mg/kg), or in combination with weekly gemcitabine (30 mg/kg). Salirasib was readily detected in mouse plasma by LC-MS/MS at a detection limit of 3 ng/mL. For each route of administration, tmax was 1 h and t1/2 ranged from 1.86 to 2.66 h. Compared to IP administration, the oral bioavailabilty of FTS was 69.5% for oral CMC and 55% for oral corn oil suspensions, while clearance and vol. of distribution were higher in both oral prepns. The orally administered salirasib inhibited panc-1 tumor growth in a dose dependent manner (67% redn. in tumor wt. at the highest dose, $P < 0.002$ vs.

control, n = 10 mice per group) and at a 40 mg/kg daily dose was synergistic with gemcitabine (83% increase in survival rate, n = 8 mice per group). Salirasib exhibits good bioavailabilty after oral administration, as detd. by a highly sensitive method for quantification in plasma. The orally available Ras inhibitor salirasib inhibited growth in nude mice, and may thus be considered for clin. trials.

Answer 14:

Bibliographic Information

Androgen Receptor Blockade in Experimental Combination Therapy of Pancreatic Cancer. Konduri, Srivani; Schwarz, Margaret A.; Cafasso, Danielle; Schwarz, Roderich E. Department of Surgery, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Divisions of Surgical Oncology and Surgical Sciences, The Cancer Institute of New Jersey, New Brunswick, NJ, USA. Journal of Surgical Research (2007), 142(2), 378-386. Publisher: Elsevier, CODEN: JSGRA2 ISSN: 0022-4804. Journal written in English. CAN 148:112427 AN 2007:1073190 CAPLUS

Abstract

Background: Reports on hormone receptor expression of pancreatic cancer (PaCa) cells and treatment responses to antihormonal therapy are still conflicting. Methods: Eight human PaCa cell lines were tested for androgen receptor (AR) protein levels by Western blot anal. Cell proliferation in vitro was measured by sulforhodamine B anal. AR agonists and inhibitors included dihydrotestosterone (DHT), testosterone (T), and flutamide (Flu). In vivo therapy of nude mouse xenografts tested Flu with gemcitabine (Gem) and/or bevacizumab (Bev). Results: Seven of eight human PaCa cell lines expressed detectable AR protein. Median relative expression

compared with the AR pos. control LnCaP was 21% (range: 16 to 63). Growth stimulation by DHT or T was minor (<20%); inhibition by Flu varied greatly and did not correlate to AR levels. Even in the sensitive cell line Panc1, Flu failed to increase Gem toxicity in vitro. However, in vivo Flu therapy resulted in significant growth inhibition of Panc-1 tumors. Flu/Gem treatment did not enhance the effect; Bev/Flu/Gem triple therapy had the greatest effect (P = 0.06 compared to Flu/Gem). Flu alone did not affect apoptotic activity, but decreased the tumor cell proliferative index (P = 0.04); in combination with Gem, Flu reduced the tumor cell d. (P = 0.02). Conclusions: The majority of PaCa cell lines express AR at various levels, but most fail to show an in vitro antiproliferative response to AR inhibition. The strong antitumor effect of flutamide in vivo is not significantly enhanced in combination with gemcitabine or bevacizumab, suggesting primarily monotherapy benefit potential of AR blockade in susceptible PaCa.

Answer 15:

Bibliographic Information

Clinical and mechanistic aspects of glucocorticoid-induced chemotherapy resistance in the majority of solid tumors. Zhang, Chengwen; Wenger, Till; Mattern, Juergen; Ilea, Septimia; Frey, Christian; Gutwein, Paul; Altevogt, Peter; Bodenmueller, Wolfram; Gassler, Nikolaus; Schnabel, Philipp A.; Dienemann, Hendrik; Marme, Alexander; Hohenfellner, Markus; Haferkamp, Axel; Pfitzenmaier, Jesco; Groene, Hermann-Josef; Kolb, Armin; Buechler, Peter; Buechler, Markus W.; Friess, Helmut; Rittgen, Werner; Edler, Lutz; Debatin, Klaus-Michael; Krammer, Peter H.; Rutz, Hans P.; Herr, Ingrid. Research Group Molecular OncoSurgery, University of Heidelberg, Heidelberg, Germany. Cancer Biology & Therapy (2007), 6(2), 278-287. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 147:479951 AN 2007:1039338 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Glucocorticoids have been used widely in conjunction with cancer therapy due to their ability to induce apoptosis in hematol. cells and to prevent nausea and emesis. However, recent data including ours, suggest induction of therapy-resistance by glucocorticoids in solid tumors, although it is unclear whether this happens only in few carcinomas or is a more common cell type specific phenomenon. We performed an overall statistical anal. of our new and recent data obtained with 157 tumor probes evaluated in vitro, ex vivo and in vivo. The effect of glucocorticoids on apoptosis, viability and cell cycle progression under diverse clin. important questions was examd. New in vivo results demonstrate glucocorticoid-induced chemotherapy resistance in xenografted prostate cancer. In an overall statistical anal. we found glucocorticoid-induced resistance in 89% of 157 analyzed tumor samples. Resistance is common for several cytotoxic treatments and for several glucocorticoid-derivs. and due to an inhibition of apoptosis, promotion of viability and cell cycle progression. Resistance occurred at clin. achievable peak plasma levels of patients under anti-emetic glucocorticoid therapy and below, lasted for a long time, after one single dose, but was reversible upon removal of glucocorticoids. Two nonsteroidal alternative anti-emetic agents did not counteract anticancer treatment and may be sufficient to replace glucocorticoids in cotreatment of carcinoma patients. These data demonstrate the need for prospective clin. studies as well as for detailed mechanistic studies of GC-induced cell-type specific pro- and anti-apoptotic signaling.

Answer 16:

Bibliographic Information

Predicting the active doses in humans from animal studies: a novel approach in oncology. Rocchetti, M.; Simeoni, M.; Pesenti, E.; De Nicolao, G.; Poggesi, I. Preclinical Development, Nerviano Medical Sciences, Nerviano, Italy. European Journal of Cancer (2007), 43(12), 1862-1868. Publisher: Elsevier Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 147:461695 AN 2007:895461 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The success rate of clin. drug development is significantly lower in oncol. than in other therapeutic areas. Predicting the activity of new compds. in humans from preclin. data could substantially reduce the no. of failures. A novel approach for predicting the expected active doses in humans from the first animal studies is presented here. The method relies upon a PK/PD model of tumor growth

inhibition in xenografts, which provides parameters describing the potency of the tested compds. Anticancer drugs, currently used in the clinic, were evaluated in xenograft models and their potency parameters were estd. A good correlation was obtained between these parameters and the exposures sustained at the therapeutically relevant dosing regimens. Based on the corresponding regression equation and the potency parameters estd. in the first preclin. studies, the therapeutically active concns. of new compds. can be estd. An early knowledge of level of exposure or doses to be reached in humans will improve the risk evaluation and decision making processes in anticancer drug development.

Answer 17:

Bibliographic Information

Determination of the optimal combination chemotherapy regimen for treatment of platinum-resistant ovarian cancer in nude mouse model. Saucier, Jenifer M.; Yu, Jiang; Gaikwad, Anjali; Coleman, Robert L.; Wolf, Judith K.; Smith, Judith A. Department of Gynecologic Oncology, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. Journal of Oncology Pharmacy Practice (2007), 13(1), 39-45. Publisher: Sage Publications Ltd., CODEN: JOPPFI ISSN: 1078-1552. Journal written in English. CAN 147:157549 AN 2007:740310 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Objective: The primary objective of this study was to evaluate the potential to increase the in vivo activity of liposomal doxorubicin when administered in combination with other chemotherapeutic agents such as topotecan, docetaxel, gemcitabine, capecitabine, or celecoxib in an ovarian cancer xenograft mouse model to identify new treatment options for recurrent platinum-sensitive/resistant ovarian cancer. Methods: This was a five-arm study in two xenograft ovarian cancer mouse models, ES-2 (platinum-sensitive), and OVCAR3 (platinum-resistant), to evaluate the combination of liposomal doxorubicin with the common chemotherapeutic agents. Each cell line had five mice for each treatment arm, five vehicle control mice, and five liposomal doxorubicin alone control mice. Expts. were done in duplicate. Results: The percentage tumor redn. ranged from 52% to 74.1% for the single-agent treatment arms. Tumor growth inhibition and regression (response) was improved on the combination treatment arms ranging from 76.1% to 100%. We obsd. increased activity in the liposomal doxorubicin plus topotecan arm, with a 27.3% improvement in response, compared with either agent alone. Conclusions: The addn. of liposomal doxorubicin demonstrated increased antitumor activity compared with either agent used alone. The most active combination treatment arm was liposomal doxorubicin with topotecan which is consistent with recent clin. study reports of enhanced activity with the combination of topoisomerase I and topoisomerase II agents. Addnl. studies are warranted to evaluate the efficacy and safety to optimize the combination of liposomal doxorubicin and topotecan for the treatment of recurrent or refractory ovarian cancer.

Answer 18:

Bibliographic Information

Magnetic poly ε-caprolactone nanoparticles containing Fe3O4 and gemcitabine enhance anti-tumor effect in pancreatic cancer xenograft mouse model. Gang, Jingu; Park, Seong-Bae; Hyung, Woochan; Choi, Eric H.; Wen, Jing; Kim, Han-Soo; Shul, Young-Gun; Haam, Seungjoo; Song, Si Young. Brain Korea 21 Project for Medical Science, Yonsei University College of Medicine, Seoul, S. Korea. Journal of Drug Targeting (2007), 15(6), 445-453. Publisher: Informa Healthcare, CODEN: JDTAEH ISSN: 1061-186X. Journal written in English. CAN 147:196939 AN 2007:721143 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The authors prepd. magnetic (Fe3O4) poly ε-caprolactone (PCL) nanoparticles (mean diam. 164±3 nm) contg. an anticancer drug (gemcitabine) using emulsion-diffusion method in order to develop more efficient drug delivery for cancer treatment. Nanoparticles were smooth, well individualized and homogeneous in size. The values of magnetizations for the magnetic PCL nanoparticles were obsd. around 10.2 emu/g at 2000 Oe magnetic field intensity and showed super-paramagnetic property. In case of the drug, the drug loading contents was 18.6% and entrapment efficiency was 52.2%. The antitumor effects caused by these particles were examd. using nude mice bearing s.c. human pancreatic adenocarcinoma cells (HPAC) in vivo. The antitumor effect was showed with 15-fold

higher dose when compared to free gemcitabine. From the result, the magnetic PCL nanoparticles may provide a therapeutic benefit by delivering drugs efficiently to magnetically targeted tumor tissues, thus achieving safe and successful antitumor effects with low toxicity.

Answer 19:

Bibliographic Information

Bcl-2-specific siRNAs restore gemcitabine sensitivity in human pancreatic cancer cells. Okamoto, Kinya; Ocker, Matthias; Neureiter, Daniel; Dietze, Otto; Zopf, Steffen; Hahn, Eckhart G.; Herold, Christoph. Department of Medicine 1, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nuernberg, Erlangen, Germany. Journal of Cellular and Molecular Medicine (2007), 11(2), 349-361. Publisher: Blackwell Publishing Ltd., CODEN: JCMMC9 ISSN: 1582-1838. Journal written in English. CAN 147:226511 AN 2007:658798 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Gemcitabine has been shown to ameliorate disease related symptoms and to prolong overall survival in pancreatic cancer. Yet, resistance to Gemcitabine is commonly obsd. in this tumor entity and has been linked to increased expression of anti-apoptotic bcl-2. We therefore investigated if and to what extend silencing of bcl-2 by specific siRNAs (siBCL2) might enhance Gemcitabine effects in human pancreatic carcinoma cells. SiBCL2 was transfected into the pancreatic cancer cell line YAP C alone and 72 h before co-incubation with different concns. of Gemcitabine. Total protein and RNA were extd. for Western-blot anal. and quant. polymerase chain reaction. Pancreatic cancer xenografts in male nude mice were treated i.p. with siBCL2 alone, Gemcitabine and control siRNA or Gemcitabine and siBCL2 for 21 days. Combination of both methods lead to a synergistic induction of apoptosis at otherwise ineffective concns. of Gemcitabine. Tumor growth suppression was also potentiated by the combined treatment with siBCL2 and Gemcitabine in vivo and lead to increased TUNEL positivity. In contrast, non-transformed human foreskin fibroblasts showed only minor responses to this treatment. Our results demonstrate that siRNA-mediated silencing of anti-apoptotic bcl-2 enhances chemotherapy sensitivity in human pancreatic cancer cells in vitro and might lead to improved therapy responses in advanced stages of this disease.

Answer 20:

Bibliographic Information

Overexpression of claudin-3 and claudin-4 receptors in uterine serous papillary carcinoma: novel targets for a type-specific therapy using Clostridium perfringens enterotoxin (CPE). Santin, Alessandro D.; Bellone, Stefania; Marizzoni, Moira; Palmieri, Michela; Siegel, Eric R.; McKenney, Jesse K.; Hennings, Leah; Comper, Fabrizio; Bandiera, Elisabetta; Pecorelli, Sergio. Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Arkansas for Medical Sciences, Little Rock, AR, USA. Cancer (Hoboken, NJ, United States) (2007), 109(7), 1312-1322. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 146:492848 AN 2007:476168 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Uterine serous papillary carcinoma (USPC) represents a highly aggressive variant of endometrial cancer. Using gene expression profiling, we recently identified high expression of the claudin-3 and claudin-4 receptors in a limited set of USPC. These tight junction proteins represent the low- and high-affinity receptors, resp., for the cytotoxic Clostridium perfringens enterotoxin (CPE) and are sufficient to mediate CPE binding and trigger subsequent toxin-mediated cytolysis. The potential for targeting this pathway in the treatment of USPC was explored. Claudin-3 and claudin-4 receptor expression was analyzed at the mRNA and protein levels in flash-frozen and formalin-fixed, paraffin-embedded tissue from 20 consecutive USPC patients. The potential of recombinant CPE as a novel therapy against primary, metastatic, and chemotherapy-resistant USPC cell lines was also investigated in vitro. Finally, the in vivo therapeutic effect of sublethal doses of CPE was studied in SCID mouse xenografts harboring s.c. and i.p. USPC that expressed claudin-3 and claudin-4. In all, 100% (20 out of 20) of the primary flash-frozen USPC tested overexpressed 1 or both CPE receptors

by quant. reverse-transcriptase polymerase chain reaction (RT-PCR). Membranous immunoreactivity for claudin-4 protein expression was documented in the majority of USPC specimens tested by immunohistochem., whereas only a low level of membranous staining was found in normal endometrial control tissue samples. When primary and metastatic short-term USPC cell lines were incubated with different concns. of CPE in vitro, a dose-dependent cytotoxic effect was demonstrated. In vivo, intratumoral injections of well-tolerated doses of CPE in large s.c. USPC xenografts led to large areas of tumor cell necrosis and tumor disappearance in all the treated animals, whereas sublethal i.p.
injections of CPE had a significant inhibitory effect on tumor progression, with extended survival of animals harboring chemotherapy-resistant intra-abdominal USPC carcinomatosis. Claudin-3 and claudin-4 receptors may offer promising targets for the use of CPE as a novel type-specific therapy against this highly aggressive and chemotherapy-resistant variant of endometrial cancer.

Answer 21:

Bibliographic Information

Effect of Epidermal Growth Factor Receptor Inhibitor Class in the Treatment of Head and Neck Cancer with Concurrent Radiochemotherapy In vivo. Feng, Felix Y.; Lopez, Carlos A.; Normolle, Daniel P.; Varambally, Sooryanarayana; Li, Xiaoxin; Chun, Patrick Y.; Davis, Mary A.; Lawrence, Theodore S.; Nyati, Mukesh K. Department of Radiation Oncology, University of Michigan Medical Center, Ann Arbor, MI, USA. Clinical Cancer Research (2007), 13(8), 2512-2518. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 147:180771 AN 2007:423505 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: To optimally integrate epidermal growth factor receptor (EGFR) inhibitors into the clin. treatment of head and neck cancer, two important questions must be answered: (a) does EGFR inhibition add to the effects of radiochemotherapy, and (b) if so, which method of inhibiting EGFR is superior (an EGFR antibody vs. a small mol. tyrosine kinase inhibitor) We designed an in vivo study to address these questions. Exptl. Design: Nude mice with UMSCC-1 head and neck cancer xenografts received either single, double, or triple agent therapy with an EGFR inhibitor (either cetuximab or gefitinib), gemcitabine, and/or radiation for 3 wk. Tumor vols. and animal wts. were measured for up to 15 wk. Immunoblotting and immunofluorescent staining were done on tumors treated with either cetuximab or gefitinib alone. Results: The addn. of an EGFR inhibitor significantly delayed the tumor vol. doubling time, from a median of 40 days with radiochemotherapy (gemcitabine and radiation) alone, to 106 days with cetuximab and 66 days with gefitinib (both $P < 0.005$). Cetuximab resulted in significantly less wt. loss than gefitinib. Immunoblot anal. and immunofluorescent staining of tumors show that although levels of phosphorylated AKT and extracellular signal-regulated kinase were decreased similarly in response to cetuximab or gefitinib, cetuximab caused prolonged suppression of pEGFR, pSTAT3, and BclXL compared with gefitinib. Conclusions: EGFR inhibition, particularly with cetuximab, improves the effectiveness of radiochemotherapy in this model of head and neck cancer. The correlation of response with prolonged suppression of EGFR, STAT3, and BclXL offers the possibility that these may be candidate biomarkers for response.

Answer 22:

Bibliographic Information

Dexamethasone as a chemosensitizer for breast cancer chemotherapy: potentiation of the antitumor activity of adriamycin, modulation of cytokine expression, and pharmacokinetics. Wang, Hui; Wang, Ying; Rayburn, Elizabeth R.; Hill, Donald L.; Rinehart, John J.; Zhang, Ruiwen. Division of Clinical Pharmacology, Department of Pharmacology and Toxicology, Gene Therapy Center, University of Alabama at Birmingham, Birmingham, AL, USA. International Journal of Oncology (2007), 30(4), 947-953. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 147:1122 AN 2007:421268 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Dexamethasone (DEX) is mainly used as an antiemetic agent in cancer therapy. We have recently demonstrated that DEX pretreatment increases the antitumor activity of the cancer chemotherapeutic agents carboplatin and gemcitabine, and decreases host toxicity in nude mouse xenograft models of human cancer. However, the underlying mechanisms are not fully understood. The present study was designed to det. the effects of DEX pretreatment on the anticancer activity of adriamycin (ADR) in a syngeneic model of breast cancer (4T1), emphasizing the effects of DEX on cytokine expression and modulation of ADR pharmacokinetics. We have demonstrated five major new findings about DEX pretreatment: (a) it enhances the therapeutic effect of ADR, inducing almost complete inhibition of tumor growth; (b) it increases tumor ADR accumulation; (c) it modulates the expression of cytokines produced by the tumor, increasing TNFα and decreasing IL-1β and VEGF expression; (d) it enhances the effects of ADR on induction of apoptosis and inhibition of cell proliferation; and (e) it suppresses nuclear NFκB activation and inhibits ADR-induced NFκB activation, possibly via IκB up-regulation. These findings suggest that DEX can be used as a chemosensitizer and chemoprotectant. These results provide a rationale for the expanded clin. use of DEX for cancer therapy.

Answer 23:

Bibliographic Information

Curcumin, a Dietary Component, Has Anticancer, Chemosensitization, and Radiosensitization Effects by Down-regulating the MDM2 Oncogene through the PI3K/mTOR/ETS2 Pathway. Li, Mao; Zhang, Zhuo; Hill, Donald L.; Wang, Hui; Zhang, Ruiwen. Department of Pharmacology and Toxicology, Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL, USA. Cancer Research (2007), 67(5), 1988-1996. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 146:372110 AN 2007:229989 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The oncoprotein MDM2, a major ubiquitin E3 ligase of tumor suppressor p53, has been suggested as a novel target for human cancer therapy based on its p53-dependent and p53-independent activities. We have identified curcumin, which has previously been shown to have anticancer activity, as an inhibitor of MDM2 expression. Curcumin down-regulates MDM2, independent of p53. In a human prostate cancer cell lines PC3 (p53null), curcumin reduced MDM2 protein and mRNA in a dose- and time-dependent manner, and enhanced the expression of the tumor suppressor p21Waf1/CIP1. The inhibitory effects occur at the transcriptional level and seem to involve the phosphatidylinositol 3-kinase/mammalian target of rapamycin/erythroblastosis virus transcription factor 2 pathway. Curcumin induced apoptosis and inhibited proliferation of PC3 cells in culture, but both MDM2 overexpression and knockdown reduced these effects. Curcumin also inhibited the growth of these cells and enhanced the cytotoxic effects of gemcitabine. When it was administered to tumor-bearing nude mice, curcumin inhibited growth of PC3 xenografts and enhanced the antitumor effects of gemcitabine and radiation. In these tumors, curcumin reduced the expression of MDM2. Down-regulation of the MDM2 oncogene by curcumin is a novel mechanism of action that may be essential for its chemopreventive and chemotherapeutic effects. Our observations help to elucidate the process by which mitogens up-regulate MDM2, independent of p53, and identify a mechanism by which curcumin functions as an anticancer agent.

Answer 24:

Bibliographic Information

Role of human longevity assurance gene 1 and C18-ceramide in chemotherapy-induced cell death in human head and neck squamous cell carcinomas. Senkal, Can E.; Ponnusamy, Suriyan; Rossi, Michael J.; Bialewski, Jacek; Sinha, Debijyati; Jiang, James C.; Jazwinski, S. Michal; Hannun, Yusuf A.; Ogretmen, Besim. Departments of Biochemistry and Molecular Biology, Medical University of South Carolina, Charleston, SC, USA. Molecular Cancer Therapeutics (2007), 6(2), 712-722. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 146:414436 AN 2007:181853 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In this study, quant. isobologram studies showed that treatment with gemcitabine and doxorubicin, known inducers of ceramide generation, in combination, supra-additively inhibited the growth of human UM-SCC-22A cells in situ. Then, possible involvement of the human homolog of yeast longevity assurance gene 1 (LASS1)/C18-ceramide in chemotherapy-induced cell death in these cells was examd. Gemcitabine/doxorubicin combination treatment resulted in the elevation of mRNA and protein levels of LASS1 and not LASS2-6, which was consistent with a 3.5-fold increase in the endogenous (dihydro)ceramide synthase activity of LASS1 for the generation of C18-ceramide. Importantly, the overexpression of LASS1 (both human and mouse homologs) enhanced the growth-inhibitory effects of gemcitabine/doxorubicin with a concomitant induction of caspase-3 activation. In reciprocal expts., partial inhibition of human LASS1 expression using small interfering RNA (siRNA) prevented cell death by about 50% in response to gemcitabine/doxorubicin. In addn., LASS1, and not LASS5, siRNA modulated the activation of caspase-3 and caspase-9, but not caspase-8, in response to this combination. Treatment with gemcitabine/doxorubicin in combination also resulted in a significant suppression of the head and neck squamous cell carcinoma (HNSCC) tumor growth in severe combined immunodeficiency mice bearing the UM-SCC-22A xenografts. More interestingly, anal. of endogenous ceramide levels in these tumors by liq. chromatog./mass spectroscopy showed that only the levels of C18-ceramide, the main product of LASS1, were elevated significantly (about 7-fold) in response to gemcitabine/doxorubicin when compared with controls. In conclusion, these data suggest an important role for LASS1/C18-ceramide in gemcitabine/doxorubicin-induced cell death via the activation of caspase-9/3 in HNSCC.

Answer 25:

Bibliographic Information

Monitoring Response to Anticancer Therapy by Targeting Microbubbles to Tumor Vasculature. Korpanty, Grzegorz; Carbon, Juliet G.; Grayburn, Paul A.; Fleming, Jason B.; Brekken, Rolf A. Hamon Center for Therapeutic Oncology Research and Departments of Surgery and Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX, USA. Clinical Cancer Research (2007), 13(1), 323-330. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 146:243146 AN 2007:8323 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: New strategies to detect tumor angiogenesis and monitor response of tumor vasculature to therapy are needed. Contrast ultrasound imaging using microbubbles targeted to tumor endothelium offers a noninvasive method for monitoring and quantifying vascular effects of antitumor therapy. We investigated the use of targeted microbubbles to follow vascular response of therapy in a mouse model of pancreatic adenocarcinoma. Exptl. Design: Microbubbles conjugated to monoclonal antibodies were used to image and quantify vascular effects of two different antitumor therapies in s.c. and orthotopic pancreatic tumors in mice. Tumor-bearing mice were treated with anti-vascular endothelial growth factor (VEGF) monoclonal antibodies and/or gemcitabine, and the localization of microbubbles to endoglin (CD105), VEGF receptor 2 (VEGFR2), or VEGF-activated blood vessels (the VEGF-VEGFR complex) was monitored by contrast ultrasound. Results: Targeted microbubbles showed significant enhancement of tumor vasculature when compared with untargeted or control IgG-targeted microbubbles. Video intensity from targeted microbubbles correlated with the level of expression of the target (CD105, VEGFR2, or the VEGF-VEGFR complex) and with microvessel d. in tumors under antiangiogenic or cytotoxic therapy. Conclusions: We conclude that targeted microbubbles represent a novel and attractive tool for noninvasive, vascular-targeted mol. imaging of tumor angiogenesis and for monitoring vascular effects specific to antitumor therapy in vivo.

Answer 26:

Bibliographic Information

Synergistic Antitumor Activity of ZD6474, An Inhibitor of Vascular Endothelial Growth Factor Receptor and Epidermal Growth Factor Receptor Signaling, with Gemcitabine and Ionizing Radiation against Pancreatic Cancer. Bianco, Cataldo; Giovannetti, Elisa; Ciardiello, Fortunato; Mey, Valentina; Nannizzi, Sara; Tortora, Giampaolo; Troiani, Teresa; Pasqualetti, Francesco; Eckhardt, Gail; de Liguoro, Mario; Ricciardi, Simona; Del Tacca, Mario; Raben, David; Cionini, Luca; Danesi, Romano. Division of Radiotherapy, Department of Oncology, Transplants and Advanced Technologies in Medicine, University of Pisa, Pisa, Italy. Clinical Cancer Research (2006), 12(23), 7099-7107. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 146:197922 AN 2006:1264178 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Std. treatments have modest effect against pancreatic cancer, and current research focuses on agents targeting mol. pathways involved in tumor growth and angiogenesis. This study investigated the interactions between ZD6474, an inhibitor of tyrosine kinase activities of vascular endothelial growth factor receptor-2 and epidermal growth factor receptor (EGFR), gemcitabine, and ionizing radiation in human pancreatic cancer cells and analyzed the mol. mechanisms underlying this combination. Exptl. Design: ZD6474, ionizing radiation, and gemcitabine, alone or in combination, were given in vitro to MIA PaCa-2, PANC-1, and Capan-1 cells and in vivo to MIA PaCa-2 tumor xenografts. The effects of treatments were studied by the evaluation of cytotoxicity, apoptosis, cell cycle, EGFR and Akt phosphorylation, modulation of gene expression of enzymes related to gemcitabine activity (deoxycytidine kinase and ribonucleotide reductase), as well as vascular endothelial growth factor immunohistochem. and microvessel count. Results: In vitro, ZD6474 dose dependently inhibited cell growth, induced apoptosis, and synergistically enhanced the cytotoxic activity of gemcitabine and ionizing radiation. Moreover, ZD6474 inhibited phosphorylation of EGFR and Akt and triggered cell apoptosis. PCR anal. showed that ZD6474 increased the ratio between gene expression of deoxycytidine kinase and ribonucleotide reductase. In vivo, ZD6474 showed significant antitumor activity alone and in combination with radiotherapy and gemcitabine, and the combination of all three modalities enhanced MIA PaCA-2 tumor growth inhibition compared with gemcitabine alone. Conclusions: ZD6474 decreases EGFR and Akt phosphorylation, enhances apoptosis, favorably modulates gene expression in cancer cells, and acts synergistically with gemcitabine and radiotherapy to inhibit tumor growth. These findings support the investigation of this combination in the clin. setting.

Answer 27:

Bibliographic Information

The development of PX-866, a novel and potent phosphoinositide-3-kinase inhibitor. Millard, Jeffrey W.; Kirkpatrick, Lynn D.; Pestano, Linda A.; Powis, Garth. Pharmaceutical Development, ProlX Pharmaceuticals, Tucson, AZ, USA. Abstracts, 19th Rocky Mountain Regional Meeting of the American Chemical Society, Tucson, AZ, United States, October 14-18 (2006), RM-091. Publisher: American Chemical Society, Washington, D. C CODEN: 69INRV Conference; Meeting Abstract written in English. AN 2006:1105335 CAPLUS

Abstract

Background: Phosphoinositide-3-kinase (PI-3-K) activates an important cell survival signaling pathway, and constitutive activation is seen in ovarian, head and neck, urinary tract, cervical and small cell lung cancer. PI-3-K signaling is attenuated by the phosphatase activity of the tumor suppressor PTEN that is absent in a no. of human cancers. Inhibiting PI-3-K presents the opportunity to inhibit a major cancer cell survival signaling pathway and to overcome the action of an important deleted tumor suppressor, providing antitumor activity and increased tumor sensitivity to a wide variety of drugs. Wortmannin is a furanosteroid fermn. product that is a known and potent PI-3-K inhibitor; however its severe hepatotoxicity and chem. instability make it an impractical pharmaceutical agent. In lieu of this, a library of 99 synthetic viridin derivs. was prepd. with the intent of increasing activity and stability while reducing assocd. toxicities. PX-866 was identified as a pharmaceutically desirable pan-PI-3-K inhibitor from the library, and it inhibits PI-3-K with IC50 of 0.1 nM and cancer cell PI-3-K with an IC50 of 20 nM. Methods: A library of C20 furan ring opened wortmannin derivs. was prepd. and screened using toxicity and activity tests including the NCI human tumor cell line panel. The antitumor activity of PX-866 was further evaluated against human tumor xenografts in scid mice, alone or in combination with taxol, gemcitabine, cisplatin, or Iressa. Results: Antitumor activity PX-866 as a single agent administered Q2D x 5 i.v. (iv) at 12 mg/kg provided OvCar-3 ovarian tumor growth inhibition (TGI = 100 - T/C %) of 58%, and at 4 mg/kg orally (po) of 53%. Conclusions: PX-866 is orally active and inhibits p-Akt survival signaling in human tumor xenografts, has antitumor activity as a single agent and potentiates the antitumor activity of a variety of cancer drugs including an EGFR-kinase inhibitor.

Answer 28:

Bibliographic Information

Antitumor Effect of Trastuzumab for Pancreatic Cancer with High HER-2 Expression and Enhancement of Effect by Combined Therapy with Gemcitabine. Kimura, Kenjiro; Sawada, Tetsuji; Komatsu, Midori; Inoue, Masafumi; Muguruma, Kazuya; Nishihara,

Tamahiro; Yamashita, Yoshito; Yamada, Nobuya; Ohira, Masaichi; Hirakawa, Kosei. Department of Surgical Oncology, Osaka City University Graduate School of Medicine, Osaka, Japan. Clinical Cancer Research (2006), 12(16), 4925-4932. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 146:265942 AN 2006:816361 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: The purpose of the present study was to evaluate whether trastuzumab has antitumor effect against pancreatic cancer and whether this effect is concordant with levels of HER-2, which is reportedly overexpressed in pancreatic cancer. We also investigated whether the effect is potentiated in combined therapy with gemcitabine. Exptl. Design: Using immunohistochem. and FACScan, we analyzed HER-2 expression in 16 pancreatic cancer cell lines. The in vitro antiproliferative effect of trastuzumab, alone and in combination with gemcitabine, was examd. by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. The in vitro antibody-dependent cell-mediated cytotoxicity of trastuzumab was investigated by 51Cr release assay. The in vivo antitumor effect of trastuzumab, alone and in combination with gemcitabine, was evaluated in nude mouse xenograft growth. The survival benefit was evaluated in a Capan-1 orthotopic implanted nude mouse model. RESULTS: HER-2 expression of 2+ or more was obsd. in 10 and of 3+ in 2 of the 16 cell lines. No in vitro growth-inhibitory effect of trastuzumab was found in any cell line, but trastuzumab induced antibody-dependent cell-mediated cytotoxicity in proportion to HER-2 expression level. Trastuzumab inhibited tumor growth in Capan-1 (HER-2: 3+) xenografts and prolonged survival in the orthotopic model. These effects were increased by combined therapy with gemcitabine. In contrast, trastuzumab exhibited no antitumor effect against PANC-1 (HER-2: 1+) or SW1990 (HER-2: 2+) xenografts. CONCLUSIONS: The antitumor effect of trastuzumab in pancreatic cancer with high HER-2 expression was shown in vitro and in vivo. Clin. application of trastuzumab is expected in pancreatic cancer with 3+ HER-2 expression.

Answer 29:

Bibliographic Information

High efficacy of combined rituximab and gemcitabine on Epstein-Barr virus-associated human B-cell lymphoma obtained after Hodgkin's xenograft in immunodeficient mice. Decaudin, Didier; Marszak, Fanny Baran; Couturier, Jerome; Mathiot, Claire; Martin, Antoine; Nemati, Fariba; Lantz, Olivier; di Santo, James; Arnaud, Philippe; Bordier, Vincent; Vincent-Salomon, Anne; Poupon, Marie-France. Department of Clinical Hematology, Section de Recherche, Institut Curie, Paris, Fr. Anti-Cancer Drugs (2006), 17(6), 685-695. Publisher: Lippincott Williams & Wilkins, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 145:202256 AN 2006:798845 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The objectives were to characterize an Epstein-Barr virus-assocd. human B-cell lymphoma obtained from Hodgkin's xenograft, and to evaluate the in-vivo combination of rituximab and/or gemcitabine. A lymph node biopsy sample from a patient with Hodgkin's disease was xenografted into Rag γ-/-c mice. Immunohistochem., cytogenetic and genetic analyses were performed on both the human biopsy and xenografted tumor from severe combined immunodeficient mice. Tumor-bearing mice were then treated with rituximab and/or gemcitabine. Histol. features of the patient's biopsy concluded on classical CD15/CD30-pos. Hodgkin's disease without expression of Epstein-Barr virus proteins. In contrast, morphol. and immunophenotypic examn. of the xenograft showed diffuse proliferation of large B cells with high Epstein-Barr virus protein expression. Comparative genomic hybridization showed a normal pattern in the first case and a gain of chromosomal 12 in the xenografted tumor. Finally, polymerase chain reaction detected an Ig heavy chain rearrangement in the xenografted tumor. Altogether, these results indicate that the xenograft grew from the patient's Epstein-Barr virus-infected B-lymphoid cells and could be assimilated to posttransplant lymphoproliferative disease. In-vivo treatments of xenografted tumors showed significant tumor growth inhibition induced either by rituximab or gemcitabine alone and an impressive efficacy of combined treatment. This result therefore indicates that combined rituximab and gemcitabine could be an alternative approach in patients with posttransplant lymphoproliferative disease.

Answer 30:

Bibliographic Information

Synergistic interaction of hyperthermia and gemcitabine in lung cancer. Vertrees, Roger A.; Das, Gokul C.; Popov, Vsevolod L.; Coscio, Angela M.; Goodwin, Thomas J.; Logrono, Roberto; Zwischenberger, Joseph B.; Boor, Paul J. Departments of Surgery, Pathology, The University of Texas Medical Branch, Galveston, TX, USA. Cancer Biology & Therapy (2005), 4(10), 1144-1153. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 145:369392 AN 2006:495293 CAPLUS

Abstract

Hyperthermia increases cytotoxicity of various antineoplastic agents. We investigated the cytotoxic effects of Gemcitabine and/or hyperthermia on BZR-T33 (human non-small-cell lung cancer cells) in vitro and in immune-suppressed athymic nude mice. Isobologram anal. of monolayer cell cultures for cytotoxicity demonstrates a synergistic interaction between hyperthermia and Gemcitabine. Clonogenic results show significant redns. in surviving fractions and colony size for both therapies; greatest redn. was for the combined therapy group. Using cell cycle anal., hyperthermia enhanced Gemcitabine-induced G2-M arrest resulting in destruction of 3.5 log cells. Apoptotic studies (Annexin-V FITC staining) showed that hyperthermia augmented Gemcitabine-induced apoptosis. Transmission electron microscopy demonstrated pathol. obsd. in cultures exposed to either therapy present in cultures exposed to both therapies. Studies in nude mice show that the combination therapy group had both an initial decrease in tumor size, and a significantly delayed rate of growth. Addnl., using tumor material harvested from nude mice two days after end to treatment reveals a significantly greater apoptotic index and significantly smaller mitotic index for the combined therapy group. Western blots of the same tumor material, showed that heat shock protein 70 was not significantly increased, however, caspase-3 activity of was significantly increased because of the combined therapy. In conclusion, the combined therapy is synergistic in effect because of hyperthermia enhancing Gemcitabine-induced apoptosis.

Answer 31:

Bibliographic Information

Potentiation of the antitumoral activity of gemcitabine and paclitaxel in combination on human breast cancer cells. Zupi, Gabriella; Scarsella, Marco; D'Angelo, Carmen; Biroccio, Annamaria; Paoletti, Giancarlo; Lopez, Massimo; Leonetti, Carlo. Experimental Chemotherapy Laboratory, Regina Elena Cancer Institute, Rome, Italy. Cancer Biology & Therapy (2005), 4(8), 866-871. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 145:347983 AN 2006:480435 CAPLUS

Abstract

The purpose of this study was to evaluate the antitumoral activity of different gemcitabine-based combination on an exptl. model of human breast cancer, in order to identify the most effective treatment and to provide a rationale for clin. investigations. To this end, CG5 breast cancer cells were treated in vitro with gemcitabine followed by epirubicin, doxorubicin, docetaxel or paclitaxel. The reversed sequence was also investigated. Results, analyzed by multiple drug effect/combination index (CI) isobologram, demonstrated that the combination gemcitabine/paclitaxel was the most active showing synergism with a CI of about 0.5 in the two sequences employed. Moreover, the synergistic interaction of gemcitabine and paclitaxel was correlated to a block of the cells in the G0/G1 compartment of cell cycle and to an increase of apoptotic cells compared to each drug. Based on these evidences, the antitumoral efficacy of gemcitabine/paclitaxel combination has been studied in vivo. Mice bearing CG5 human breast xenografts treated with paclitaxel and gemcitabine in combination showed a significant higher inhibition of tumor growth (.apprx.70%) compared to that with either agent alone (25%). In conclusion, this study suggests that paclitaxel is the most promising agent for combination protocols with gemcitabine and supports the use of gemcitabine/paclitaxel combination in the clin. management of advanced breast cancer.

Answer 32:

Bibliographic Information

A modified random oligonucleotide-based combination therapy for adjuvant treatment on pancreatic ductal

adenocarcinoma. Tepel, Juergen; March, Christina; Ketterer, Thomas; Kapischke, Matthias; Arlt, Alexander; Kremer, Bernd; Kalthoff, Holger; Kruse, Marie-Luise. Departments of General Surgery and Thoracic Surgery, University Hospital Schleswig-Holstein, Kiel, Germany. International Journal of Oncology (2006), 28(5), 1105-1112. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 146:54830 AN 2006:464091 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Anti-cancer therapy in pancreatic ductal adenocarcinoma (PDAC) is mostly based on surgical removal or palliative therapy using antimetabolites, like 5'-fluorouracil or gemcitabine. Adjuvant treatment using these chemotherapeutics has recently proven a beneficial concept, though general survival rates are still poor. Most recently, combination therapy of gemcitabine with other targeted drugs was evaluated in clin. trials. We present here a study performed in a mouse orthotopic xenotransplant model of PDAC, using an oligonucleotide-based approach. We have shown previously that antisense oligonucleotides against p53 reduce the wt. of orthotopic pancreatic tumors in immune-deficient mice. We further characterized terminal modifications of phosphorothioate oligonucleotides in vitro and found a random, unrelated control sequence carrying a D,L-α-tocopherol modification at the 5' and 3' ends to be most efficient in induction of cell death in PancTu-1 cells. Modified random oligonucleotide (MRON) were thus further tested in vivo. MRON showed a redn. of tumor wt. in established primary orthotopic tumors in SCID/bg mice. In a surgically adapted pre-clin. model, where primary tumors were resected and animals received adjuvant treatment, MRON was very efficient in suppression of relapse and metastasis, when combined with gemcitabine. While the exact mol. mechanism of MRON activity still needs to be elucidated, the compd. showed a remarkable preference for uptake into tumor cells in vivo.

Answer 33:

Bibliographic Information

Corticosteroid co-treatment induces resistance to chemotherapy in surgical resections, xenografts, and established cell lines of pancreatic cancer. Zhang, Chengwen; Kolb, Armin; Buechler, Peter; Cato, Andrew C. B.; Mattern, Juergen; Rittgen, Werner; Edler, Lutz; Debatin, Klaus-Michael; Buechler, Markus W.; Friess, Helmut; Herr, Ingrid. Research Group Molecular Urooncology, German Cancer Research Center, Heidelberg, Germany. BMC Cancer (2006), 6 No pp. given. Publisher: BioMed Central Ltd., CODEN: BCMACL ISSN: 1471-2407. http://www.biomedcentral.com/content/pdf/1471-2407-6-61.pdf Journal; Online Computer File written in English. CAN 144:425939 AN 2006:314605 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Chemotherapy for pancreatic carcinoma often has severe side effects that limit its efficacy. The glucocorticoid (GC) dexamethasone (DEX) is frequently used as co-treatment to prevent side effects of chemotherapy such as nausea, for palliative purposes and to treat allergic reactions. While the potent pro-apoptotic properties and the supportive effects of GCs to tumor therapy in lymphoid cells are well studied, the impact of GCs to cytotoxic treatment of pancreatic carcinoma is unknown. Methods: A prospective study of DEX-mediated resistance was performed using a pancreatic carcinoma xenografted to nude mice, 20 surgical resections and 10 established pancreatic carcinoma cell lines. Anti-apoptotic signaling in response to DEX was examd. by Western blot anal. Results: In vitro, DEX inhibited drug-induced apoptosis and promoted the growth in all of 10 examd. malignant cells. Ex vivo, DEX used in physiol. concns. significantly prevented the cytotoxic effect of gemcitabine and cisplatin in 18 of 20 freshly isolated cell lines from resected pancreatic tumors. No correlation with age, gender, histol., TNM and induction of therapy resistance by DEX co-treatment could be detected. In vivo, DEX totally prevented cytotoxicity of chemotherapy to pancreatic carcinoma cells xenografted to nude mice. Mechanistically, DEX upregulated pro-survival factors and anti-apoptotic genes in established pancreatic carcinoma cells. Conclusions: These data show that DEX induces therapy resistance in pancreatic carcinoma cells and raise the question whether GC-mediated protection of tumor cells from cancer therapy may be dangerous for patients.

Answer 34:

Bibliographic Information

Molecular mechanism of phenoxodiol-induced apoptosis in ovarian carcinoma cells. Alvero, Ayesha B.; O'Malley, David; Brown, David; Kelly, Graham; Garg, Manish; Chen, Wei; Rutherford, Thomas; Mor, Gil. Department of Obstetrics & Gynecology, Yale University School of Medicine, New Haven, CT, USA. Cancer (Hoboken, NJ, United States) (2006), 106(3), 599-608. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 145:76157 AN 2006:155201 CAPLUS

Abstract

Previously, it was demonstrated that phenoxodiol induces apoptosis in epithelial ovarian carcinoma (EOC) cells and that it is capable of sensitizing these cells to Fas-mediated apoptosis. The objectives of this study were to det. whether phenoxodiol can also act as chemosensitizer to chemotherapeutic agents and to characterize the mol. mechanism behind its sensitizing effect. Ten EOC cell lines were used in this study. The effect of phenoxodiol on the inhibitory concn. 50% (IC50) of carboplatin, paclitaxel, and gemcitabine was detd. by the CellTiter 96 Assay. The in vivo effect of combination treatments with phenoxodiol and the above-mentioned agents was detd. in animal xenograft models. Apoptosis was measured using the Caspase-Glo Assay and the apoptotic cascade was characterized by Western blot analyses. The results showed that phenoxodiol is able to sensitize EOC cells to carboplatin, paclitaxel, and gemcitabine both in vitro and in vivo. In addn., it was demonstrated that phenoxodiol is capable of inducing apoptosis by: (1) the activation of the mitochondrial pathway through caspase-2 and Bid signaling, and (2) the proteasomal degrdn. of the anti-apoptotic protein XIAP. Understanding the components of the apoptotic pathway activated by phenoxodiol, which allows it to sensitize EOC cells to chemotherapeutic agents, will provide valuable information on the characteristic mode of action of a chemosensitizer. This will help in the identification of novel drugs and in the design of better strategies for combination therapy in patients with recurrent ovarian carcinoma.

Answer 35:

Bibliographic Information

Glucocorticoid-mediated inhibition of chemotherapy in ovarian carcinomas. Zhang, Chengwen; Marme, Alexander; Wenger, Till; Gutwein, Paul; Edler, Lutz; Rittgen, Werner; Debatin, Klaus-Michael; Altevogt, Peter; Mattern, Juergen; Herr, Ingrid. Molecular Urooncology, German Cancer Research Center, Heidelberg, Germany. International Journal of Oncology (2006), 28(2), 551-558. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 145:95902 AN 2006:150417 CAPLUS

Abstract

The glucocorticoid dexamethasone is frequently used as a co-treatment in cytotoxic cancer therapy, e.g. to prevent nausea, to protect normal tissue or for other reasons. While the potent pro-apoptotic properties and supportive effects of glucocorticoids to tumor therapy in lymphoid cells are well studied, the impact on the cytotoxic treatment of ovarian carcinoma is unknown. We tested apoptosis-induction, viability, tumor growth and protein expression using established cell lines, primary cell lines freshly isolated from patient material and a xenograft on nude mice. We found a general induction of resistance toward cytotoxic therapy by DEX-co-treatment in most of the examd. ovarian cancer cells treated in vitro, ex vivo or in vivo. Resistance occurred independently of cell d. and was found at peak plasma levels of dexamethasone and below. Mechanistically, the dexamethasone-induced expression of survival genes may be involved in the resistance. These data show that glucocorticoid-induced resistance is common in ovarian carcinomas implicating that the use of glucocorticoids may be harmful for cancer patients.

Answer 36:

Bibliographic Information

Synergistic Effects of Gemcitabine and Gefitinib in the Treatment of Head and Neck Carcinoma. Chun, Patrick Y.; Feng, Felix Y.; Scheurer, Ashley M.; Davis, Mary A.; Lawrence, Theodore S.; Nyati, Mukesh K. Department of Radiation Oncology, University of Michigan Medical School, Ann Arbor, MI, USA. Cancer Research (2006), 66(2), 981-988. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 144:100392 AN

2006:55803 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Although the combination of gemcitabine and radiation produces a high frequency of complete responses in the treatment of locally advanced head and neck cancer, substantial toxicity suggests that an improvement in the therapeutic index is required. The purpose of this study was to det. if gefitinib could improve the efficacy of gemcitabine and if drug schedule is important. We hypothesized that gemcitabine followed by gefitinib would be superior to the opposite order because of both cell cycle and growth factor signaling interactions. Using UMSCC-1 cells in vitro, we confirmed that gefitinib arrested cells in G1 and suppressed phospho-epidermal growth factor receptor (pY845EGFR) and that gemcitabine arrested cells in S phase and stimulated pY845EGFR. The schedule of gemcitabine followed by gefitinib caused arrest of cells in S phase. Gefitinib suppressed gemcitabine-mediated pY845EGFR stimulation. This schedule caused decreased pS473AKT, increased poly(ADP-ribose) polymerase cleavage, and increased apoptosis compared with gemcitabine alone. The schedule of gefitinib followed by gemcitabine also caused suppression of pY845EGFR but arrested cells in G1. This schedule in which gefitinib was used first was assocd. with stable levels of pS473AKT and minimal poly(ADP-ribose) polymerase cleavage and apoptosis. These results were reflected in expts. in nude mice bearing UMSCC-1 xenografts, in which there was greater tumor regression and apoptosis when animals received gemcitabine followed by gefitinib during the first week of therapy. These findings suggest that the schedule of gemcitabine followed by gefitinib may increase the therapeutic index over gemcitabine alone and, combined with clin. data, encourage exploration of combination of gemcitabine, EGFR inhibitors, and radiation.

Answer 37:

Bibliographic Information

Enhanced efficacy of gemcitabine in combination with anti-CD20 monoclonal antibody against CD20+ non-Hodgkin's lymphoma cell lines in vitro and in scid mice. Smith, Mitchell R.; Joshi, Indira; Jin, Fang; Obasaju, Coleman. Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA. BMC Cancer (2005), 5 No pp. given. Publisher: BioMed Central Ltd., CODEN: BCMACL ISSN: 1471-2407. http://www.biomedcentral.com/content/pdf/1471-2407-5-103.pdf Journal; Online Computer File written in English. CAN 144:16578 AN 2005:1174712 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Despite exciting new targeted therapeutics against non-Hodgkin's lymphoma (NHL), chemotherapy remains a cornerstone of therapy. While purine nucleoside analogs have significant activity in low grade NHL, the pyrimidine nucleoside analog gemcitabine has been less extensively studied, but has important activity. Use of the anti-CD20 monoclonal antibody rituximab in combination with chemotherapy for B-NHL is becoming prevalent in clin. practice, but has not been extensively studied in pre-clin. models. We have tested the activity of gemcitabine ± rituximab in vitro and in scid/human NHL xenograft models. We used two t(14;18)+, CD20+ follicular B cell NHL cell lines, DoHH2 a transformed NHL line and WSU-FSCCL isolated from pleural fluid of a patient with indolent NHL. Gemcitabine is cytotoxic to DoHH2 and WSU-FSCCL cells in vitro, and the IC50 is 2-3 fold lower in the presence of rituximab. Apoptosis is also enhanced in the presence of rituximab. Clearance of NHL cells from ascites in scid mice is prolonged by the combination, as compared with either agent alone. Most importantly, survival of scid mice bearing human NHL cells is significantly prolonged by the combination of gemcitabine + rituximab. Based on our pre-clin. data showing prolonged survival of mice bearing human lymphoma cell line xenografts after treatment with gemcitabine + anti-CD20 antibody, this combination, expected to have non-overlapping toxicity profiles, should be explored in clin. trials.

Answer 38:

Bibliographic Information

The anti-tumor effect of Apo2L/TRAIL on patient pancreatic adenocarcinomas grown as xenografts in SCID mice. Hylander, Bonnie L.; Pitoniak, Rose; Penetrante, Remedios B.; Gibbs, John F.; Oktay, Dilek; Cheng, Jinrong; Repasky, Elizabeth A. Department of Immunology, Roswell Park Cancer Institute, Buffalo, NY, USA. Journal of Translational Medicine (2005), 3 No

pp. given. Publisher: BioMed Central Ltd., CODEN: JTMOBV ISSN: 1479-5876.
http://www.translational-medicine.com/content/pdf/1479-5876-3-22.pdf Journal; Online Computer File written in English. CAN 143:210436 AN 2005:799811 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Apo2L/TRAIL has considerable promise for cancer therapy based on the fact that this member of the tumor necrosis factor family induces apoptosis in the majority of malignant cells, while normal cells are more resistant. Furthermore, in many cells, when Apo2L/TRAIL is combined with chemotherapy, the effect is synergistic. The majority of this work has been carried out using cell lines. Thus, investigation of how patient tumors respond to Apo2L/TRAIL can validate and/or complement information obtained from cell lines and prove valuable in the design of future clin. trials. The authors investigated the Apo2L/TRAIL sensitivity of patient-derived pancreatic tumors using a patient tumor xenograft SCID mouse model. Mice bearing engrafted tumors were treated with Apo2L/TRAIL, gemcitabine or a combination of both therapies. Patient tumors grown as xenografts exhibited a spectrum of sensitivity to Apo2L/TRAIL. Both Apo2L/TRAIL sensitive and resistant pancreatic tumors were found, as well as tumors that showed heterogeneity of response. Changes in apoptotic signaling mols. in a sensitive tumor were analyzed by Western blot following Apo2L/TRAIL treatment; loss of procaspase 8, Bid, and procaspase 3 was obsd. and correlated with inhibition of tumor growth. However, in a tumor that was highly resistant to killing by Apo2L/TRAIL, although there was a partial loss of procaspase 8 and Bid in response to Apo2L/TRAIL treatment, loss of procaspase 3 was negligible. This resistant tumor also expressed a high level of the anti-apoptotic mol. Bcl-XL that, in comparison, was not detected in a sensitive tumor. Importantly, in the majority of these tumors, addn. of gemcitabine to Apo2L/TRAIL resulted in a greater anti-tumor effect than either therapy used alone. Thus, in a clin. setting one will see heterogeneity in the response of patients' tumors to Apo2L/TRAIL, including tumors that are highly sensitive as well as those that are resistant.

It is very encouraging that Apo2L/TRAIL in combination with gemcitabine increased therapeutic efficacy in almost every case and therefore may be a highly effective strategy for controlling human pancreatic cancer.

Answer 39:

Bibliographic Information

Fluvastatin synergistically enhances the antiproliferative effect of gemcitabine in human pancreatic cancer MIAPaCa-2 cells.
Bocci, G.; Fioravanti, A.; Orlandi, P.; Bernardini, N.; Collecchi, P.; Del Tacca, M.; Danesi, R. Division of Pharmacology and Chemotherapy, University of Pisa, Pisa, Italy. British Journal of Cancer (2005), 93(3), 319-330. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 143:452269 AN 2005:693433 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The new combination between the nucleoside analog gemcitabine and the cholesterol-lowering drug fluvastatin was investigated in vitro and in vivo on the human pancreatic tumor cell line MIAPaCa-2. The present study demonstrates that fluvastatin inhibits proliferation, induces apoptosis in pancreatic cancer cells harboring a p21ras mutation at codon 12 and synergistically potentiates the cytotoxic effect of gemcitabine. The pharmacol. activities of fluvastatin are prevented by administration of mevalonic acid, suggesting that the shown inhibition of geranyl-geranylation and farnesylation of cellular proteins, including p21rhoA and p21ras, plays a major role in its anticancer effect. Fluvastatin treatment also indirectly inhibits the phosphorylation of p42ERK2/mitogen-activated protein kinase, the cellular effector of ras and other signal transduction peptides. Moreover, fluvastatin administration significantly increases the expression of the deoxycytidine kinase, the enzyme required for the activation of gemcitabine, and simultaneously reduces the 5'-nucleotidase, responsible for deactivation of gemcitabine, suggesting a possible addnl. role of these enzymes in the enhanced cytotoxic activity of gemcitabine. Finally, a significant in vivo antitumor effect on MIAPaCa-2 xenografts was obsd. with the simultaneous combination of fluvastatin and gemcitabine, resulting in an almost complete suppression and a marked delay in relapse of tumor growth. In conclusion, the combination of fluvastatin and gemcitabine is an effective cytotoxic, proapoptotic treatment in vitro and in vivo against MIAPaCa-2 cells by a mechanism of action mediated, at least in part, by the inhibition of p21ras and rhoA prenylation. The obtained exptl. findings might constitute the basis for a novel translational research in humans.

Answer 40:

Bibliographic Information

Expression of Bcl-xL in ovarian carcinoma is associated with chemoresistance and recurrent disease. Williams, Jennifer; Lucas, Peter C.; Griffith, Kent A.; Choi, Milheon; Fogoros, Sarah; Hu, Yuan Yuan; Liu, J. Rebecca. Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA. Gynecologic Oncology (2005), 96(2), 287-295. Publisher: Elsevier, CODEN: GYNOA3 ISSN: 0090-8258. Journal written in English. CAN 143:37973 AN 2005:66520 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Objective: The long-term survival of patients with epithelial ovarian cancer is limited by the emergence of tumor cells that are resistant to chemotherapy. We hypothesized that expression of Bcl-xL, a homolog of Bcl-2 that confers protection from chemotherapy-induced apoptosis, may be predictive of patients' clin. response to treatment, and that treatment with chemotherapy may result in the selection of tumor cells that overexpress this protein. Methods: We detd. the expression of Bcl-xL in epithelial ovarian cancers from 28 patients at the time of initial staging laparotomy and in recurrent tumors in the same patients following treatment with platinum-based chemotherapy. The data were analyzed to det. whether Bcl-xL expression was predictive of clin. outcome. A2780 ovarian cancer cells were stably transfected with Bcl-xL or control plasmid. Chemotherapy-induced apoptosis in these cell lines was detd. in vitro and in a xenograft model. Results: Bcl-xL expression in primary tumors was assocd. with a significantly shorter disease-free interval as compared to patients whose tumors did not express Bcl-xL (1.6 mo as compared to 7.7 mo). We found that Bcl-xL expression conferred resistance to chemotherapy-induced apoptosis resulting from treatment with cisplatin, paclitaxel, topotecan, and gemcitabine in vitro. In a xenograft model, Bcl-xL expressing tumors continued to grow following treatment with cisplatin, paclitaxel, topotecan, and gemcitabine, in contrast to control tumors, which disappeared. Conclusions: These results portray an important role for Bcl-xL as a key factor assocd. with chemotherapy failure in the treatment of ovarian cancer.

Answer 41:

Bibliographic Information

Incorporation of OSI-7836 into DNA of Calu-6 and H460 xenograft tumors. Richardson, Frank; Black, Chris; Richardson, Katherine; Franks, April; Wells, Edward; Karimi, Susan; Sennello, Gina; Hart, Karen; Meyer, Denny; Emerson, David; Brown, Eric; LeRay, Jeremy; Nilsson, Christy; Tomkinson, Blake; Bendele, Raymond. OSI Pharmaceuticals, Inc., Boulder, CO, USA. Cancer Chemotherapy and Pharmacology (2005), 55(3), 213-221. Publisher: Springer GmbH, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 142:329107 AN 2005:10437 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

OSI-7836 (4'-thio-β-d-arabinofuranosylcytosine) is a novel nucleoside analog in phase I clin. development for the treatment of cancer. As with other nucleoside analogs, the proposed mechanism of action involves phosphorylation to the triphosphate form followed by incorporation into cellular DNA, leading to cell death. This hypothesis has been examd. by measuring and comparing the incorporation of ara-C, OSI-7836, and gemcitabine (dFdC) into DNA of cultured cells and by investigating the role of deoxycytidine kinase in OSI-7836 toxicity. We report here addnl. studies in which the role of cell cycling on OSI-7836 toxicity was investigated and incorporation of OSI-7836 into DNA of xenograft tumors measured. The role of the cell cycle was examd. by comparing the toxicity of OSI-7836 in A549 NSCLC cells that were either in log phase growth or had reached confluence. A novel validated LC-MS/MS assay was developed to quantify the concns. of OSI-7836 in DNA from Calu-6 and H460 human tumor xenografts in mice. Results showed that apoptosis induced by OSI-7836 was markedly greater in cycling cells than in confluent non-cycling cells despite only a modest increase in intracellular OSI-7836 triphosphate concn. The LC-MS/MS assay developed to measure OSI-7836 incorporation into DNA had an on-column detection limit of 0.25 fmol, a quantification limit of 0.5 fmol, and a sensitivity of approx. 0.1 pmol OSI-7836/μmol dThy. Concns. of OSI-7836 in splenic DNA (0.4 pmol OSI-7836/μmol dThy) averaged fivefold less than the av. concn. in Calu-6 and H460 xenograft DNA (3.0 pmol OSI-7836/μmol dThy) following a 400 mg/kg dose of OSI-7836. Concns. of OSI-7836 in Calu-6 tumor DNA isolated 24 h following a dose of 400, 1000, or 1600 mg OSI-7836/kg were approx. 1.3, 1 and 1.3 pmol OSI-7836/μmol dThy, resp. Concns. of OSI-7836 in DNA from H460 and Calu-6 xenografts did not appear to increase during repeated administration of 400 mg OSI-7836/kg on days 1, 4, 7, and 10.

The majority of OSI-7836 in DNA from Calu-6 and H460 tumors of mice dosed with 1600 mg/kg was located at internal nucleotide linkages, similar to dFdC and ara-C. In conclusion, cell cycling studies supported the hypothesis that OSI-7836 cytotoxicity is dependent upon DNA synthesis. A validated LC-MS/MS assay was developed that could quantify OSI-7836 in DNA from tissues. The assay was used to show that OSI-7836 was incorporated in internal linkages in tumor DNA in a manner that was dose-independent at the doses tested and did not appear to accumulate during repeated dosing. The results suggest that if DNA incorporation is a toxic event, the relationships between administered dose, DNA incorporation, and toxicity are complex.

Answer 42:

Bibliographic Information

Antiproliferative Activity and Mechanism of Action of Fatty Acid Derivatives of Gemcitabine in Leukemia and Solid Tumor Cell Lines and in Human Xenografts. Bergman, A. M.; Kuiper, C. M.; Noordhuis, P.; Smid, K.; Voorn, D. A.; Comijn, E. M.; Myhren, F.; Sandvold, M. L.; Hendriks, H. R.; Fodstad, O.; Breistol, K.; Peters, G. J. Department Medical Oncology, VU University Medical Center, Amsterdam, Neth. Nucleosides, Nucleotides & Nucleic Acids (2004), 23(8 & 9), 1329-1333. Publisher: Marcel Dekker, Inc., CODEN: NNNAFY ISSN: 1525-7770. Journal written in English. CAN 142:148062 AN 2004:913123 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Gemcitabine is a deoxycytidine analog, which can be inactivated by deamination catalyzed by deoxycytidine deaminase (dCDA). Altered transport over the cell membrane is a mechanism of resistance to gemcitabine. To facilitate accumulation, the fatty acid deriv. CP-4125 was synthesized. Since, the fatty acid is acylated at the site of action of dCDA, a decreased deamination was expected. CP-4125 was equally active as gemcitabine in a panel of rodent and human cell lines and in human melanoma xenografts bearing mice. In contrast to gemcitabine, CP-4125 was not deaminated but inhibited deamination of deoxycytidine and gemcitabine. Pools of the active triphosphate of gemcitabine increased for over 20 h after CP-4125 exposure, while these pools decreased directly after removal of gemcitabine. In conclusion: CP-4125 is an interesting new gemcitabine deriv.

Answer 43:

Bibliographic Information

Microregional Effects of Gemcitabine in HCT-116 Xenografts. Huxham, Lynsey A.; Kyle, Alastair H.; Baker, Jennifer H. E.; Nykilchuk, Lani K.; Minchinton, Andrew I. Department of Medical Biophysics, British Columbia Cancer Research Centre, Vancouver, BC, Can. Cancer Research (2004), 64(18), 6537-6541. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 141:253981 AN 2004:757680 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To examine the tumor microregional effects after gemcitabine administration to mice, the authors mapped the location of proliferating and hypoxic cells relative to vasculature in human colon cancer xenografts. The S-phase marker bromodeoxyuridine was used as a surrogate of drug effect and administered 2 h before tumor excision, whereas vessel position and perfusion were assessed via staining for CD31 and i.v. injection of carbocyanine, resp. Hypoxia was detected using pimonidazole. Images of the four markers were overlaid to reveal the spatial relationship between proliferation, vasculature, and hypoxia and to examine the microregional effects. Within 1 day after administration of 240 mg/kg of gemcitabine, proliferation throughout the tumor was completely inhibited. Over time, a reemergence of dividing cells occurred in relation to the distance from vasculature. Microregional anal. revealed that cells located distal to vasculature commenced cycling sooner than cells located proximal to vasculature. A similar trend was seen after multiple doses of gemcitabine (40 mg/kg on days 1, 4, 7, and 10). The possibility that the effect of gemcitabine could be attributed to changes in oxygenation was discounted after examg. the vessel perfusion and patterns of hypoxia. The effect of gemcitabine was examd. in multilayered cell culture, and at doses <30 μmol/L, a gradient in proliferation between the exposed and unexposed sides was obsd. The

authors show a differential effect on cell proliferation in relation to vasculature and conclude that cells distal to blood vessels are less affected by gemcitabine probably because of limited penetration.

Answer 44:

Bibliographic Information

Anti-tumor and anti-angiogenic activity of heterocycle-bridged fused pyrroloindenocarbazoles. Underiner, Ted L.; Ruggeri, Bruce A.; Aimone, Lisa; Angeles, Thelma S.; Gessner, George; Hellriegel, Edward; Robinson, Candy; Singh, Jasbir; Yang, Shi X. Department of Medicinal Chemistry, Cephalon, Inc, West Chester, PA, USA. Abstracts of Papers, 228th ACS National Meeting, Philadelphia, PA, United States, August 22-26, 2004 (2004), MEDI-091. Publisher: American Chemical Society, Washington, D. C CODEN: 69FTZ8 Conference; Meeting Abstract written in English. AN 2004:657955 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A series of heterocycle-bridged fused pyrroloindenocarbazoles (1) were prepd. and evaluated against a panel of kinases (e.g., trkA, VEGFR-2, PDGFR-β, PKC, and InRK). Preliminary pharmacokinetic properties of these carbazoles revealed that potent trkA inhibitor (2) possessed an oral bioavailability of 19% (rat). Compd. 2 displayed significant growth inhibition of human and murine prostate carcinoma xenografts in nude mice, synergistic enhancement of survival in an orthotopic pancreatic tumor model when used in combination with gemcitabine and showed dose related anti-angiogenic activity when evaluated ex vivo (rat aortic ring explant model) as well as in vivo (PAEC-VEGF/bFGF Matrigel implant model).

Answer 45:

Bibliographic Information

Overexpression of Bid increases the therapeutic effect of gemcitabine on ductal pancreatic adenocarcinoma in an orthotopic SCID mouse xenotransplantation model. Trauzold, A.; Kapischke, M.; Emme, D.; Sipos, B.; Tepel, J.; Roeder, C.; Kremer, B.; Kalthoff, H. Forschungsgruppe Molekulare Onkologie, Universitaetsklinikum Schleswig-Holstein, Germany. Chirurgisches Forum fuer Experimentelle und Klinische Forschung (2004), 129-131. Publisher: Springer-Verlag, CODEN: CFEKA7 ISSN: 0303-6227. Journal written in German. CAN 141:150617 AN 2004:597784 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Pancreatic adenocarcinoma is one of the most aggressive cancer types with an extremely poor prognosis. Inability to die by apoptosis is one of the reasons for the deregulated growth of tumor cells and the frequently obsd. failure of chemotherapy. Recently, the authors found several anti-apoptotic proteins being up-regulated in apoptosis-resistant pancreatic adenocarcinoma cell lines, whereas some pro-apoptotic proteins were clearly down-regulated. Among the pro-apoptotic proteins the authors found that the mitochondrial apoptosis pathway inducing protein, Bid, was strongly down-regulated in resistant PancTul and Panc89 cells. In this study the authors investigated the role of Bid in the apoptotic pathway triggered by the chemotherapeutic agent gemcitabine. In order to construct an isogenic cellular system for Bid investigation, the authors retrovirally transduced Panc89 and PancTuI cells with a Bid-expression vector and an empty vector, resp., and detd. the Bid expression by Western Blot. For quantification of the gemcitabine-mediated apoptotic cell death in vitro the JAM - and EZ4U-Assays were used. The effect of Bid-overexpression on gemcitabine therapeutic efficacy was tested in vivo using an orthotopic mouse xenotransplantation model in SCID-beige mice. The gemcitabine doses used were 2.5 or 20 mg/kg bodyweight/day. The overexpression of Bid in both apoptosis resistant cell lines showed a strongly enhanced effect on the death receptor (CD95 and TRAILR) but not on the gemcitabine-mediated apoptosis in vitro. In the orthotopic tumor model the Bid overexpressing cells developed clearly smaller tumors under gemcitabine treatment compared to wild type cells or cells transfected with an empty vector. The authors could show that an overexpression of Bid led to an improvement of the gemcitabine therapy.

Interestingly, the authors found significant discrepancies between the role of Bid in gemcitabine-mediated apoptosis in vitro and in vivo, a phenomenon that could possibly be explained by the role of the tumor stroma in the effectiveness of

anti-cancer therapy.

Answer 46:

Bibliographic Information

Resistance to gemcitabine in a human follicular lymphoma cell line is due to partial deletion of the deoxycytidine kinase gene. Galmarini, Carlos Maria; Clarke, Marilyn L.; Jordheim, Lars; Santos, Cheryl L.; Cros, Emeline; Mackey, John R.; Dumontet, Charles. INSERM 590 - Lab. Cytologie Analytique, Fac. med. Rockefeller, Univ. Claude Bernard Lyon, Lyon, Fr. BMC Pharmacology (2004), 4 No pp. given. Publisher: BioMed Central Ltd., CODEN: BPMHBU ISSN: 1471-2210. http://www.biomedcentral.com/content/pdf/1471-2210-4-8.pdf Journal; Online Computer File written in English. CAN 141:235865 AN 2004:504490 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Gemcitabine is an analog of deoxycytidine with activity against several solid tumors. To elucidate the mechanisms by which tumor cells become resistant to gemcitabine, we developed the resistant subline RL-G from the human follicular lymphoma cell line RL-7 by prolonged exposure of parental cells to increasing concns. of gemcitabine. Results: In vitro, the IC50 increased from 0.015 μgM in parental RL-7 cells to 25 μ.M in the resistant variant, RL-G. Xenografts of both cell lines developed in nude mice were treated with repeated injections of gemcitabine. Under conditions of gemcitabine treatment which totally inhibited the development of RL-7 tumors, RL-G derived tumors grew similarly to those of untreated animals, demonstrating the in vivo resistance of RL-G cells to gemcitabine. HPLC expts. showed that RL-G cells accumulated and incorporated less gemcitabine metabolites into DNA and RNA than RL-7 cells. Gemcitabine induced an S-phase arrest in RL-7 cells but not in RL-G cells. Exposure to gemcitabine induced a higher degree of apoptosis in RL-7 than in RL-G cells, with poly-(ADP-ribose) polymerase cleavage in RL-7 cells. No modifications of Bcl-2 nor of Bax expression were obsd. in RL-7 or RL-G cells exposed to gemcitabine. These alterations were assocd. with the absence of the deoxycytidine kinase mRNA expression obsd. by quant. RT-PCR in RL-G cells. PCR amplification of deoxycytidine kinase gene exons showed a partial deletion of the dCK gene in RL-G cells. Conclusions: These results suggest that partial deletion of the dCK gene obsd. after selection in the presence of gemcitabine is involved with resistance to this agent both in vitro and in vivo.

Answer 47:

Bibliographic Information

Effect of LY293111 in combination with gemcitabine in colonic cancer. Hennig, Rene; Ding, Xian-Zhong; Tong, Wei-Gang; Witt, Richard C.; Jovanovic, Borko D.; Adrian, Thomas E. Department of Surgery and Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Tarry Building, Northwestern University, Chicago, IL, USA. Cancer Letters (Amsterdam, Netherlands) (2004), 210(1), 41-46. Publisher: Elsevier, CODEN: CALEDQ ISSN: 0304-3835. Journal written in English. CAN 141:46881 AN 2004:444127 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

New adjuvant therapies are needed for the treatment of stage III colon cancer. The essential fatty acids, linoleic and arachidonic acid enhance tumorigenesis through the cyclooxygenase and lipoxygenase pathways. Leukotriene B4 (LTB4) is a product of 5-lipoxygenase (5-LOX) which has tumor-promoting effects. The LTB4 receptor antagonist, LY293111 inhibited tumor growth and induced apoptosis in vitro. The effectiveness of LY293111, alone and in combination with gemcitabine was investigated in a heterotopic xenograft model in athymic mice using HT29 and LoVo human colon cancer cells. The combined therapy markedly inhibited tumor growth and could warrant consideration as a new therapeutic option.

Answer 48:

Bibliographic Information

Inhibition of Src tyrosine kinase impairs inherent and acquired gemcitabine resistance in human pancreatic adenocarcinoma cells. Duxbury, Mark S.; Ito, Hiromichi; Zinner, Michael J.; Ashley, Stanley W.; Whang, Edward E. Brigham and Women's Hospital, Department of Surgery, Harvard Medical School, Boston, MA, USA. Clinical Cancer Research (2004), 10(7), 2307-2318. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:360258 AN 2004:290908 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We tested the hypotheses that Src tyrosine kinase overactivity represents a chemoresistance mechanism and that Src inhibition may enhance gemcitabine cytotoxicity in pancreatic adenocarcinoma cells. Pancreatic adenocarcinoma cells PANC1, MiaPaCa2, Capan2, BxPC3, and PANC1GemRes, a stably gemcitabine-resistant subline of PANC1, were exposed to combinations of gemcitabine and Src tyrosine kinase inhibitor 4-amino-5-(4-chlorophenyl)-7-(t-butyl)pyrazolo[3,4-d]pyrimidine (PP2). Src expression, phosphorylation (Tyr-416), and activity were analyzed by immunoblotting and in vitro kinase assay. Expression of the M2 subunit of ribonucleotide reductase (RRM2), a putative chemoresistance enzyme, was quantified by Northern and Western blot. Cellular proliferation was quantified by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. Apoptosis was characterized by YO-PRO-1/propidium iodide staining, fluorometric caspase profiling, and caspase inhibition (Z-Val-Ala-Asp-fluoromethyl ketone). The effects of constitutively active and dominant neg. Src were detd. The therapeutic efficacy of PP2 in combination with gemcitabine was tested in nude mice orthotopically xenografted with PANC1GemRes. Greater gemcitabine resistance was assocd. with higher Src phosphorylation and activity, both of which were higher in PANC1GemRes, relative to PANC1; total Src levels were alike. PANC1GemRes overexpressed RRM2. PP2 enhanced inherent gemcitabine chemosensitivity and attenuated gemcitabine resistance in PANC1GemRes. Constitutively active Src increased gemcitabine chemoresistance; dominant neg. Src impaired gemcitabine chemoresistance. PP2 augmented gemcitabine-induced caspase-mediated apoptosis, suppressed RRM2 expression, and decreased activity of the RRM2-regulating transcription factor E2F1 in PANC1GemRes. PP2 and gemcitabine in combination substantially decreased tumor growth and inhibited metastasis in vivo.

Increased Src tyrosine kinase activity represents a potential chemoresistance mechanism and a promising therapeutic target warranting further investigation in gemcitabine-resistant pancreatic adenocarcinoma.

Answer 49:

Bibliographic Information

Clonogenic assay with established human tumour xenografts: correlation of in vitro to in vivo activity as a basis for anticancer drug discovery. Fiebig, H. H.; Maier, A.; Burger, A. M. Oncotest GmbH, Institute for Experimental Oncology, Freiburg, Germany. European Journal of Cancer (2004), 40(6), 802-820. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 141:342988 AN 2004:284718 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Pluripotent cells can be grown in clonogenic assays. The tumor stem-cell fraction, which accounts for <0.4% of the total cells, and which is considered the most relevant cell type in the development of metastases and recurrences, is able to divide and to form colonies in a semisolid matrix (agar or methylcellulose). Major applications of the tumor clonogenic assay (TCA) are chemosensitivity testing of tumors and xenografts, and for assessments within drug discovery programs. Of crit. relevance for the usefulness of the TCA is whether it can predict sensitivity or resistance towards clin. used agents. When we compared the response of human tumors established as xenografts in nude mice in the TCA in vitro to that of the clin. response, 62% of the comparisons for drug sensitivity, and 92% of the comparisons for drug resistance were correct. The same percentage of true/false observations was found when tumors were tested after serial passage in nude mice in the TCA in vitro and their response compared to in vivo activity in corresponding xenografts (60% and 90%, resp.). The highest correct predictive values were, however, found when the clin. response of tumors was compared to their explants established in the nude mouse and treated in vivo. Of 80 comparisons performed, we obsd. a correct prediction for tumor resistance in 97% and for tumor sensitivity in 90%. In our opinion, the TCA with established human tumor xenografts has an important role in current drug discovery strategies. We therefore included the TCA as secondary assay in our approach to anticancer drug discovery and found that a no. of novel agents were active; these are now in advanced preclin. development or clin. trials. Thus, the tumor clonogenic assay has proven predictive value in the chemosensitivity testing of std. and

exptl. anticancer drugs.

Answer 50:

Bibliographic Information

Combined 90yttrium-DOTA-labeled PAM4 antibody radioimmunotherapy and gemcitabine radiosensitization for the treatment of a human pancreatic cancer xenograft. Gold, David V.; Modrak, David E.; Schutsky, Keith; Cardillo, Thomas M. Center for Molecular Medicine and Immunology, Garden State Cancer Center, Belleville, NJ, USA. International Journal of Cancer (2004), 109(4), 618-626. Publisher: Wiley-Liss, Inc., CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 141:220966 AN 2004:274115 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have examd. the application of 90Y-DOTA-cPAM4, anti-MUC1 IgG, in combination with the front-line drug gemcitabine as a potential therapeutic for pancreatic cancer. Athymic nude mice bearing CaPan1 human pancreatic cancer xenografts were administered 2 mg of gemcitabine on days 0, 3, 6, 9 and 12 with concurrent 90Y-DOTA-cPAM4 (100 μCi) provided on day 0. A second group of mice received a second cycle of treatment 5 wk after the start of the first cycle. Control groups of mice included those that received either treatment arm alone, the combined modality treatment employing a nontargeting control antibody (hLL2, anti-B-cell lymphoma) and a final group that was left untreated. Gemcitabine administered as a single agent provided no antitumor effect. A single cycle of the combined 90Y-DOTA-cPAM4 and gemcitabine treatment provided greater inhibition of tumor growth than was obsd. for any of the other treatment procedures. Tumor growth was delayed for a period of 7 wk. Two cycles of gemcitabine with concomitant 90Y-DOTA-cPAM4 yielded significant tumor regression and increased median survival to 21 wk vs. 12 wk for mice receiving a single cycle of therapy ($p<0.024$). Median tumor vol. doubling-times were 18 wk in mice treated with 2-cycles of therapy vs. 7 wk in mice given only 1-cycle ($p<0.001$), and 3.5 wk for the group that received 2-cycles of gemcitabine concomitant with equitoxic nontargeting 90Y-DOTA-hLL2 ($p<0.001$). These data suggest that addn. of 90Y-DOTA-cPAM4 RAIT to a gemcitabine treatment regimen may provide enhanced antitumor efficacy for the treatment of pancreatic cancer.

Answer 51:

Bibliographic Information

Activity of irofulven against human pancreatic carcinoma cell lines in vitro and in vivo. van Laar, Emily S.; Roth, Stephanie; Weitman, Steven; MacDonald, John R.; Waters, Stephen J. MGI Pharma, Inc., Bloomington, MN, USA. Anticancer Research (2004), 24(1), 59-65. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 141:253867 AN 2004:255466 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Irofulven (MGI 114), a novel antitumor agent synthesized from the natural product illudin S, has a unique mechanism of action involving macromol. adduct formation, S-phase arrest and induction of apoptosis. This study utilized MiaPaCa pancreatic xenografts to demonstrate irofulven antitumor activity using either a daily or intermittent dosing schedule. Addnl., irofulven and gemcitabine were tested in vitro and in vivo to assess the anticancer activity of the combination. Both dosing regimens of irofulven demonstrated curative activity against the MiaPaCa xenografts. Similar activity of irofulven on the intermittent schedule was obsd. at lower total doses compared to the daily dosing schedule. Furthermore, enhanced antitumor activity was obsd. when irofulven and gemcitabine were combined compared to single agent activity. These results support further clin. characterization of intermittent irofulven dosing schedules and suggest that irofulven combined with gemcitabine may have activity in patients with pancreatic tumors.

Answer 52:

Bibliographic Information

Pretreatment with dexamethasone increases antitumor activity of carboplatin and gemcitabine in mice bearing human cancer Xenografts: in vivo activity, pharmacokinetics, and clinical implications for cancer chemotherapy. Wang, Hui; Li, Mao; Rinehart, John J.; Zhang, Ruiwen. Department of Pharmacology and Toxicology, Division of Clinical Pharmacology, University of Alabama at Birmingham, Birmingham, AL, USA. Clinical Cancer Research (2004), 10(5), 1633-1644. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:307750 AN 2004:194636 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The present study was undertaken to det. the effects of dexamethasone (DEX) pretreatment on antitumor activity and pharmacokinetics of the cancer chemotherapeutic agents carboplatin and gemcitabine. Antitumor activities of carboplatin and gemcitabine with or without DEX pretreatment were detd. in six murine-human cancer xenograft models, including cancers of colon (LS174T), lung (A549 and H1299), and breast (MCF-7 and MDA-MB-468) and glioma (U87-MG). Effects of DEX on plasma and tissue pharmacokinetics of carboplatin and gemcitabine were also detd. by using the LS174T, A549, and H1299 models. Although DEX alone showed minimal antitumor activity, DEX pretreatment significantly increased the efficacy of carboplatin, gemcitabine, or a combination of both drugs by 2-4-fold in all xenograft models tested. Without DEX treatment, the tumor exposure to carboplatin, measured by the area under the curve, was markedly lower than normal tissues. However, DEX pretreatment significantly increased tumor carboplatin levels, including 200% increase in area under the curve, 100% increase in max. concn., and 160% decrease in clearance. DEX pretreatment similarly increased gemcitabine uptake in tumors. .To our knowledge, this is the first report that DEX significantly enhances the antitumor activity of carboplatin and gemcitabine and increases their accumulation in tumors. These results provide a basis for further evaluation of DEX as a chemosensitizer in patients.

Answer 53:

Bibliographic Information

Inhibition of platelet-derived growth factor receptor phosphorylation by STI571 (Gleevec) reduces growth and metastasis of human pancreatic carcinoma in an orthotopic nude mouse model. Hwang, Rosa F.; Yokoi, Kenji; Bucana, Corazon D.; Tsan, Rachel; Killion, Jerald J.; Evans, Douglas B.; Fidler, Isaiah J. Departments of Cancer Biology and. Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA. Clinical Cancer Research (2003), 9(17), 6534-6544. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:81779 AN 2003:1009874 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We evaluated the expression of platelet-derived growth factor (PDGF) ligands and receptors in clin. specimens of human pancreatic adenocarcinomas and detd. the therapeutic effect of STI571 (Gleevec), a protein tyrosine kinase inhibitor of PDGF receptor (PDGFR), on human pancreatic carcinoma cells growing in the pancreas and liver of nude mice. Immunohistochem. staining for PDGF-AA and -BB ligands, PDGFR-α and -β, and phosphorylated PDGFR-α and -β was performed on 31 specimens of human pancreatic cancer and L3.6pl human pancreatic adenocarcinoma cell line. To det. the in vivo effects of STI571, nude mice with L3.6pl cells injected into the pancreas were randomized 7 days later to receive one of the following treatments: sterile water p.o. (control), STI571, gemcitabine, or a combination of STI571 and gemcitabine. In 29 of 31 clin. specimens of human pancreatic adenocarcinoma, both tumor cells and tumor-assocd. endothelial cells expressed phosphorylated PDGFR-α and -β. L3.6pl cells growing in culture expressed moderate amts. of PDGF-AA and little to no PDGFR-α or -β, whereas L3.6pl cells growing in the pancreas of nude mice expressed a high level of PDGF and receptors. Colocalization immunohistochem. anal. demonstrated expression of activated PDGFR-β by tumor-assocd. endothelial cells in both the pancreas and in liver metastases. Tumors of mice treated for 4 wk with STI571 (50 mg/kg or 100 mg/kg p.o. daily) were slightly smaller than controls. Tumors treated with gemcitabine and STI571 (50 mg/kg) were > 70% smaller than tumors in control mice and 36% smaller than those in mice treated with gemcitabine only ($P < 0.0002$ and $P < 0.04$, resp.). Combination therapy also inhibited spontaneous metastasis to the liver. Tumors from mice treated with both STI571 and gemcitabine had decreased expression of activated (phosphorylated) PDGFR-α and -β, decreased mean vessel d., decreased cell proliferation, and increased apoptosis of tumor cells.

Collectively, these data show that activated PDGFR on tumor cells and tumor-endothelial cells can be a novel target for therapy of pancreatic carcinoma.

Answer 54:

Bibliographic Information

Low-dose radioimmunotherapy (90Y-PAM4) combined with gemcitabine for the treatment of experimental pancreatic cancer. Gold, David V.; Schutsky, Keith; Modrak, David; Cardillo, Thomas M. Garden State Cancer Center, Belleville, NJ, USA. Clinical Cancer Research (2003), 9(10, Pt. 2), 3929s-3937s. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 140:402408 AN 2003:847733 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Monoclonal antibody PAM4 is reactive with the MUC1 mucin as expressed by >85% of human pancreatic cancers. Significant antitumor effects have been demonstrated using radiolabeled PAM4 for radioimmunotherapy (RAIT) of exptl. pancreatic cancer. The goal of the present study was to det. whether the addn. of low-dose 90Y-PAM4 RAIT to a clin. relevant regimen of gemcitabine chemotherapy would provide enhanced antitumor efficacy over that obsd. by chemotherapy alone without the addn. of significant toxicity to normal tissues. Exptl. Design: Mice bearing human pancreatic tumor xenografts (CaPan1) were administered three cycles of gemcitabine chemotherapy (1000 mg/m2/wk for 3 wk with 1 wk off) concomitant with 90Y-labeled PAM4 RAIT (25 μCi; 10% of the single agent MTD) given at weeks 0, 4, and 7. Control groups of mice received chemotherapy alone, 90Y-PAM4 RAIT alone, or an equidose of 90Y-labeled nontargeting control antibody with and without gemcitabine. Results: Mice that received 90Y-PAM4 RAIT with gemcitabine had tumors that were significantly smaller in size than all of the other treatment groups ($P < 0.005$). A median survival of 24 wk was achieved in mice that received the combined treatment vs. 10 wk for mice that received only gemcitabine ($P < 0.001$) and 16 wk for mice that received only 90Y-PAM4 RAIT ($P < 0.040$). The combined treatment regimen was well tolerated. Conclusions: A combined chemoimmunotherapy and RAIT approach using gemcitabine and low-dose 90Y-PAM4 provided significantly increased antitumor efficacy than was obsd. for each treatment arm given alone. Importantly, the enhanced antitumor efficacy was achieved with minimal toxicity to normal tissues. These studies provide justification for clin. trials using the combined modality treatment for patients with pancreatic cancer.

Answer 55:

Bibliographic Information

Combination therapy with pretarget CC49 radioimmunotherapy and gemcitabine prolongs tumor doubling time in a murine xenograft model of colon cancer more effectively than either monotherapy. Graves, Scott S.; Dearstyne, Erica; Lin, Yukang; Zuo, Yuting; Sanderson, James; Schultz, Jody; Pantalias, Anastasia; Gray, David; Axworthy, Don; Jones, H. Mark; Auditore-Hargreaves, Karen. NeoRx Corporation, Seattle, WA, USA. Clinical Cancer Research (2003), 9(10, Pt. 1), 3712-3721. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 140:419941 AN 2003:847705 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Pretarget radioimmunotherapy (RIT) is a multistep strategy for cancer therapy designed to reduce nontarget organ exposure by uncoupling the tumor targeting moiety from the radioactive ligand. Using this approach, we and others have demonstrated objective responses to therapy among patients with non-Hodgkin's lymphoma, with less hematol. toxicity than is typically seen at equiv. doses of conventional RIT in the same patient population. In the present study, we show that combination therapy with gemcitabine (200 mg/kg on days -1 and +1) and Pretarget RIT (400 μCi 90Y-labeled DOTA-biotin on day +1) is superior to Pretarget monotherapy (400 or 800 μCi 90Y) as well as to gemcitabine monotherapy in nude mice bearing established human LS174T colon cancer xenografts. For the targeting moiety, we used a murine anti-TAG-72 (CC49) single-chain Fv-streptavidin (scFvSA) fusion protein that has been shown to be safe and well-tolerated in humans. The median no. of days to tumor vol. doubling in the gemcitabine-only studies (200 mg/kg) was 10.4 ± 5.5 days; in the Pretarget 400 μCi dose-only studies, tumor doubling time was 6.7 ± 4.9 days; and in combination therapy studies, it was 23.9 ± 7.2 days ($P \leq 0.0001$ vs. Pretarget or gemcitabine monotherapy). There were no consistently significant differences among the two monotherapy regimens and the combination therapy regimen with respect to peripheral blood cell counts, nor were there significant differences in bone marrow colony-forming activity among the three treatment groups. These data indicate

that gemcitabine can be combined with Pretarget RIT to increase antitumor response, without increasing hematol. toxicity, in a murine xenograft model.

Answer 56:

Bibliographic Information

Effects of the epidermal growth factor receptor inhibitor OSI-774, tarceva, on downstream signaling pathways and apoptosis in human pancreatic adenocarcinoma. Ng, Sylvia S. W.; Tsao, Ming-Sound; Nicklee, Trudey; Hedley, David W. Divisions of Experimental Therapeutics, Ontario Cancer Institute, Medical Biophysics, Princess Margaret Hospital and University of Toronto, Toronto, ON, Can. Molecular Cancer Therapeutics (2002), 1(10), 777-783. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 139:46544 AN 2003:57578 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Pancreatic cancer is the fifth leading cause of cancer death in North America. Gemcitabine improves the quality of life of patients but fails to significantly reduce mortality. Our lab. has demonstrated previously that the phosphatidylinositol 3'-kinase inhibitor wortmannin promotes gemcitabine antitumor. The present study examd. the effects of the epidermal growth factor receptor (EGFR) inhibitor OSI-774 ("Tarceva") alone and in combination with wortmannin and/or gemcitabine on downstream signaling mols., as well as apoptosis in primary pancreatic cancer xenografts implanted orthotopicaly in severely combined immunodeficient mice. Tumors established from two pancreatic cancer patients [Ontario Cancer Institute Pancreas no. (OCIP#) 2 and OCIP#7] were treated with various combinations of the above three drugs and harvested for analyses of the following: the levels of phosphorylated and nonphosphorylated forms of EGFR, protein kinase B (PKB/Akt) and extracellular-regulated kinase (ERK1/2), and the extent of apoptosis using immunofluorescence image anal. and TUNEL assay, resp. OSI-774 alone significantly inhibited phosphorylation of EGFR in both of the primary xenografts. Phosphorylation of pERK decreased in OCIP#2, but not in OCIP#7. No significant effects on pPKB because of OSI-774 were obsd. in either tumor type. The extent of apoptosis was significantly increased by 2-fold in OCIP#2 tumors treated with gemcitabine and wortmannin in combination; an addnl. 2-fold increase in apoptosis was evident in the presence of OSI-774. Although wortmannin failed to enhance gemcitabine-induced apoptosis in OCIP#7 tumors, the extent of apoptosis was significantly increased with the inclusion of OSI-774 in the combination. Taken together, these findings support the use of OSI-774 plus a phosphatidylinositol 3'-kinase inhibitor in combination with gemcitabine in the treatment of pancreatic cancer.

Answer 57:

Bibliographic Information

Treatment of pancreatic cancer xenografts with Erbitux (IMC-C225) anti-EGFR antibody, gemcitabine, and radiation. Buchsbaum, Donald J.; Bonner, James A.; Grizzle, William E.; Stackhouse, Murray A.; Carpenter, Mark; Hicklin, Daniel J.; Bohlen, Peter; Raisch, Kevin P. Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, AL, USA. International Journal of Radiation Oncology, Biology, Physics (2002), 54(4), 1180-1193. Publisher: Elsevier Science Inc., CODEN: IOBPD3 ISSN: 0360-3016. Journal written in English. CAN 139:32573 AN 2002:839606 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: To investigate treatment of human pancreatic cancer cell lines and xenografts with combinations of Erbitux (IMC-C225) anti-epidermal growth factor receptor (EGFR) antibody, gemcitabine, and radiation. Methods and Materials: BxPC-3 and MiaPaCa-2 human pancreatic carcinoma cells were treated in vitro for 24 h with IMC-C225 (5 μg/mL), then exposed to epidermal growth factor (EGF) (10 mM) for 5 min. Immunoblots were screened for EGFR expression and the ability of IMC-C225 to block EGF-induced tyrosine phosphorylation of EGFR. Cells were treated with IMC-C225 (5 μg/mL) on Day 0, the IC50 dose of gemcitabine on Day 1 for 24 h, followed by 3 Gy 60Co irradn. on Day 2, or the combination of each agent. For cell proliferation, cells were counted on Day 4, and for apoptosis, cells were stained with annexin V-FITC and propidium iodide, then analyzed by FACS. Cells were treated with the

same single or multiple treatments and analyzed in a clonogenic cell survival assay. The effect of IMC-C225, gemcitabine, and radiation on the growth of BxPC-3 and MiaPaCa-2 tumor xenografts was detd. Athymic nude mice bearing established s.c. tumor xenografts of 6-8 mm diam. received 6 wk of treatment with IMC-C225 (1 mg every 3 days × 6) alone or in combination with gemcitabine (120 mg/kg i.v. every 6 days × 6), and 6 weekly fractions of 3 Gy radiation on the days after gemcitabine administration. Tumor growth was measured with Vernier calipers. Results: BxPC-3 and MiaPaCa-2 cell lines expressed low levels of EGFR. IMC-C225 inhibited EGF-induced tyrosine phosphorylation of the EGF receptor on both cell lines. Treatment of cells with a combination of IMC-C225 + gemcitabine + radiation produced the highest induction of apoptosis and inhibition of proliferation in vitro. Combination treatment with IMC-C225, gemcitabine, and radiation produced 100% complete regression of MiaPaCa-2 tumors for more than 250 days, and the greatest growth inhibition of BxPC-3 tumors compared to any single or dual treatments.
Conclusions: The IMC-C225 therapy in combination with gemcitabine chemotherapy and radiation therapy demonstrated statistically significantly greater efficacy over the single and double combination therapies. This form of multimodality treatment shows potential clin. application in the treatment of pancreatic cancer in humans.

Answer 58:

Bibliographic Information

A Phase I Trial of Weekly Gemcitabine and Subcutaneous Interferon Alpha in Patients with Refractory Renal Cell Carcinoma. Perez-Zincer, F.; Olencki, T.; Budd, G. T.; Peereboom, D.; Elson, P.; Bukowski, R. M. Department of Hematology and Medical Oncology, The Cleveland Clinic Foundation, Cleveland, OH, USA. Investigational New Drugs (2002), 20(3), 305-310. Publisher: Kluwer Academic Publishers, CODEN: INNDDK ISSN: 0167-6997. Journal written in English. CAN 138:198224 AN 2002:512415 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Introduction: Recombinant human interferon-α2b (rHuIFN-α2b) and interleukin-2 have limited effectiveness in the treatment of metastatic renal cell carcinoma (MRCC). Gemcitabine (Gemzar) is also reported to have activity against MRCC, and recent in vitro, in nude mice xenografts, and human data suggests increased activity of Gemcitabine (Gemzar) when combined with IFN-α2b. Purpose: A phase I clin. trial utilizing Gemcitabine (Gemzar) and rHuIFN-α2b was conducted in patients with metastatic renal cell carcinoma. Methods: Treatment consisted of: Gemcitabine (Gemzar) 600 mg/m2 i.v. weekly and rHuIFN-α2b 1.0 MU/m2 (dose level A) or 3.0 MU/m2 s.c. (dose level B) 3 times a week for 6 wk with a 2-wk rest period. Results: Thirteen patients were entered into the trial and were evaluated. Dose-limiting toxicity was predominantly hematol., and was seen at dose level B. This included grade 3 anemia (1 patient), neutropenia (1 patient), and nausea (1 patient) and grade 4 neutropenia (1 patient). The maximal tolerated dose was Gemcitabine (Gemzar) 600 mg/m2 i.v. weekly and rHuIFN-α2b 1.0 MU/m2 3 times a week. Conclusion: This combination of Gemcitabine (Gemzar) and rHuIFN-α2b has significant hematol. toxicity despite low doses of each agent. Further investigation of this combination using this schedule is not recommended.

Answer 59:

Bibliographic Information

Antitumor activity of combination treatment with gemcitabine and topotecin against human lung cancer xenografted in nude mice. Fujita, Fumiko; Koike, Masako; Fujita, Masahide. Experimental Cancer and Chemotherapy Research Lab. Ltd., Mino-shi, Osaka, Japan. Gan to Kagaku Ryoho (2002), 29(4), 577-584. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 137:362616 AN 2002:367485 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Gemcitabine is a new deoxycytidine deriv. that shows a distinguishing, potent antitumor activity against various human tumor lines transplanted to nude mice. We have investigated the antitumor activity of gemcitabine combined with cisplatin (CDDP) or vindesine (VDS) using a lung cancer line, H-74, that was insensitive to almost all antitumor drugs and relatively insensitive to gemcitabine. We

found that the antitumor effects of gemcitabine combined with CDDP or VDS were more potent and lasted longer than that of each drug alone, without an increase in side effects such as body wt. loss. In this study, the antitumor activity of combined gemcitabine with topotecin (CPT 11) was evaluated using a similar method for 8 wk, including a 4-wk treatment period and a subsequent 4-wk drug-free period, with ref. to tumor growth inhibition rate, histol. changes, and side effects. The treatment combining gemcitabine with CPT-11 administered at each 1/2 MTD showed an additive effect at 4 and 8 wk after start of administration. Furthermore, no remarkable side effects were obsd. Since these study results demonstrated that gemcitabine combined with CPT-11 increased and prolonged the antitumor activity without increasing side effects such as bodyweight loss, it is expected that CPT-11 could be one of the useful drugs used in combination with gemcitabine for lung cancer therapy.

Answer 60:

Bibliographic Information

Wortmannin inhibits PKB/Akt phosphorylation and promotes gemcitabine antitumor activity in orthotopic human pancreatic cancer xenografts in immunodeficient mice. Ng, Sylvia S. W.; Tsao, Ming-Sound; Nicklee, Trudey; Hedley, David W. Divisions of Experimental Therapeutics, Ontario Cancer Institute, Princess Margaret Hospital and University of Toronto, Toronto, ON, Can. Clinical Cancer Research (2001), 7(10), 3269-3275. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 137:27870 AN 2001:799817 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Pancreatic cancer is resistant to almost all classes of cytotoxic agents. Gemcitabine seems to be the current drug of choice. The authors have recently reported that inhibition of the phosphatidylinositide 3-kinase-protein kinase B (PKB/Akt) cell survival pathway by wortmannin enhances gemcitabine-induced apoptosis in cultured human pancreatic cancer cells. The present study investigated the effects of wortmannin on orthotopic human pancreatic cancer xenografts implanted in severe combined immunodeficient mice. Animals were given single i.v. bolus injections of 0.175, 0.35, or 0.7 mg/kg of wortmannin and killed at 0.5, 1, 2, or 4 h after treatment. Phosphorylated PKB/Akt levels in tumor tissues were measured by fluorescence image anal. Wortmannin was found to inhibit PKB/Akt phosphorylation in a time- and dose-dependent manner, reaching a plateau at 4 h and at 0.7 mg/kg. The levels of phosphorylated PKB/Akt were maximally decreased by .apprx.50% relative to the vehicle control. Subsequently, the extent of apoptosis in tumors treated with gemcitabine or wortmannin alone or in combination was detd. using terminal deoxynucleotidyl transferase-mediated nick end labeling assay and computerized image anal. Orthotopic tumors exposed to 80 mg/kg gemcitabine for 48 h and then 0.7 mg/kg wortmannin for 4 h showed a 5-fold increase in apoptosis compared with those treated with each agent alone and with the vehicle control. The combination treatment also significantly inhibited tumor growth. Taken together, the authors' findings support the potential of phosphatidylinositide 3-kinase inhibitors as adjuncts to conventional chemotherapy in the treatment of pancreatic cancer.

Answer 61:

Bibliographic Information

The efficacy of 2',2'-difluorodeoxycytidine (gemcitabine) and vinblastine combined with interferon in nude mice xenografts of human renal cell carcinoma. Rohde, Detlef; Goertz, Markus; Blatter, Johannes; Jakse, Gerhard. Department of Urology, Medical Faculty, University of Aachen, Aachen, Germany. International Journal of Oncology (1998), 12(6), 1367-1372. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 129:144586 AN 1998:366966 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Recent in vitro expts. indicated strong activity of 2',2'-difluorodeoxycytidine (dFdC, gemcitabine) in human renal cell carcinoma (RCC) cell lines and an increase of efficacy by combined application of interferon (IFN). In the present study, nude mice with xenografts from ACHN- or SN12C cells were treated by dFdC, dFdC plus IFN-α or vinblastine (VBL) plus IFN-α. ACHN-xenografts were significantly more inhibited by dFdC+/-IFN-α than by VBL+IFN-α. Complete remissions (CR) were only seen by dFdC. An addnl.

treatment with IFN-α shortened the time to commencement of tumor remission and increased CR of ACHN- and SN12C-tumors (40%; 7%) compared to a treatment with dFdC alone (20%; 0). DFdC+IFN-α reduced the no. of pulmonary metastases compared to untreated animals. Survival was significantly prolonged by dFdC+/-IFN-α in ACHN-mice and dFdC+IFN-α or VBL+IFN-α in SN12C mice. In conclusion, exptl. data confirm dFdC as a superior drug against human RCC compared to VBL. Combined therapy with IFN-α increased the efficacy of dFdC in terms of tumor response in immunodeficient nude mice, thus clin. studies are strongly recommended in patients with metastatic renal cell carcinoma.

Answer 62:

Bibliographic Information

Enhancement of radiation-induced regrowth delay by gemcitabine in a human tumor xenograft model. Joschko, Marion A.; Webster, Lorraine K.; Groves, Janice; Yuen, Kally; Palatsides, Manuela; Ball, David L.; Millward, Michael J. Experimental Chemotherapy and Pharmacology Unit, Trescowthick Research Laboratories, Peter MacCallum Cancer Institute, Melbourne, Australia. Radiation Oncology Investigations (1997), 5(2), 62-71. Publisher: Wiley-Liss, CODEN: ROINEU ISSN: 1065-7541. Journal written in English. CAN 127:202230 AN 1997:564083 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Gemcitabine, a cytidine nucleoside analog, has schedule-dependent antitumor activity in vitro and in vivo. Gemcitabine also has dose- and time-dependent radiosensitization properties in vitro. Thus it may have therapeutic application in combination with radiation. The aims of this study were to investigate whether gemcitabine could enhance radiation-induced tumor regrowth delay in a human squamous carcinoma (FaDu) xenograft in nude mice and to examine the effect of gemcitabine on radiation-induced apoptosis in in vivo tumors. X-rays were given locally to the tumors twice daily in 2 Gy fractions over 2 wk for 5 days/wk. Significant regrowth delay enhancement was obsd. which was dependent on gemcitabine schedule. Effective schedules using max. tolerated gemcitabine doses were twice weekly and once weekly, but not daily. Significant toxicity occurred with radiation plus twice weekly gemcitabine, but enhancement was seen using gemcitabine doses well below the max. tolerated dose. Both gemcitabine and radiation led to apoptotic cell death, but this was not increased when both treatments were combined. These results indicate that gemcitabine may be of therapeutic value as a radiation enhancer in the treatment of human cancers. Preliminary studies suggest that increased apoptotic cell death is not a mechanism leading to this enhancement.

Answer 63:

Bibliographic Information

The influence of BIBW22BS, a dipyridamole derivative, on the antiproliferative effects of 5-fluorouracil, methotrexate and gemcitabine in vitro and in human tumor xenografts. Jansen, W. J. M.; Pinedo, H. M.; Van Der Wilt, C. L.; Feller, N.; Bamberger, U.; Boven, E. Department Medical Oncology, Amsterdam, Neth. European Journal of Cancer, Part A (1995), 31A(13/14), 2313-19. Publisher: Elsevier, CODEN: EJCTEA Journal written in English. CAN 124:249952 AN 1996:139911 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Dipyridamole is known as a potent inhibitor of facilitated diffusion-mediated nucleoside transport as well as a modulator of "classical" multidrug resistance. BIBW22BS, a deriv. of dipyridamole, has been found to be 20- to 100-fold more potent in the reversal of multidrug resistance when compared to the parent compd. In parallel, we studied the efficacy of BIBW22BS in the modulation of the antiproliferative effects of 5-fluorouracil, methotrexate and gemcitabine in human cancer cell lines. BIBW22BS, at non-toxic concns. up to 1.0 μM, increased the antiproliferative effects of 5-fluorouracil 2- to 6-fold in seven of the eight colon cancer cell lines tested in a dose-dependent manner. The addn. of 1.0 μM BIBW22BS to methotrexate resulted in a slight increase in the antiproliferative effects, but inhibited the activity of gemcitabine 30- to 100-fold in various cancer cell lines. In vitro, no notable difference was found between BIBW22BS and dipyridamole in their capacity to modulate the activity of the antimetabolites studied. BIBW22BS did not affect the growth inhibition induced by 5-fluorouracil or gemcitabine in human tumor xenografts grown s.c. in nude mice. We confirmed the higher potency of BIBW22BS when compared to dipyridamole in the reversal of drug resistance in the Pgp-pos. COLO 320 cell line

Answer 64:

Bibliographic Information

Interaction between cisplatin and gemcitabine in vitro and in vivo. Peters, Godefridus J.; Bergman, Andre M.; Ruiz van Haperen, Veronique W. T.; Veerman, Gijsbert; Kuiper, Carin M.; Braakhuis, Boudewijn J. M. Department Oncology, Free University Hospital, Amsterdam, Neth. Seminars in Oncology (1995), 22(4, Suppl. 11), 72-9. Publisher: Saunders, CODEN: SOLGAV ISSN: 0093-7754. Journal written in English. CAN 124:75591 AN 1995:955488 CAPLUS

Abstract

A possible synergism between the 2 title drugs was studied: in vitro by using 3 variants of the human ovarian cancer cell line A2780, and in vivo in mice by using gemcitabine- and cisplatin-sensitive and -resistant tumors: the head and neck cancer xenografts HNX-22B and HNX-14C and the murine syngeneic colon 26-10 tumor. In vitro, cells were cultured for 72 h and exposed to the drugs for 1-72 h; synergy was evaluated by multiple drug-effect anal. In wild-type A2780 and cisplatin-resistant ADDP cells, simultaneous exposure for 24 and 72 h was synergistic, as was preincubation with cisplatin for 4 h followed by gemcitabine. Preincubation with gemcitabine for 4 h followed by gemcitabine and cisplatin was synergistic in ADDP and A2780 cells. Cisplatin did not enhance the accumulation of gemcitabine triphosphate in A2780 and ADDP cells. Cisplatin caused a marginal decrease of the no. of double-strand breaks in the DNA caused by gemcitabine. In vivo, gemcitabine at the max. tolerated dose of 100 or 120 mg/kg could be combined with cisplatin at 4 mg/kg. Simultaneous injection of this combination resulted in at least additive antitumor activity in HNX-22B, but not in HNX-14C and colon 26-10, tumors. Cisplatin, injected 4 h before or after gemcitabine, was as active against HNX-22B tumors as when given simultaneously with gemcitabine, but was more toxic. In conclusion, the combination of gemcitabine and cisplatin can be synergistic in vitro and at least additive in vivo; this synergism is schedule dependent. The mechanism does not involve gemcitabine triphosphate accumulation or DNA damage.

Answer 65:

Bibliographic Information

Schedule-dependent antitumor effect of gemcitabine in in vivo model systems. Braakhuis, Boudewijn J. M.; Van Haperen, Veronique W. T. Ruiz; Boven, Epie; Veerman, Gijsbert; Peters, Godefridus J. Department Otolaryngology/Head and Neck Surgery, Free University Hospital, Amsterdam, Neth. Seminars in Oncology (1995), 22(4, Suppl. 11), 42-6. Publisher: Saunders, CODEN: SOLGAV ISSN: 0093-7754. Journal written in English. CAN 124:75740 AN 1995:955483 CAPLUS

Abstract

The therapeutic effects of gemcitabine at the max. tolerated dose level are dependent on the administration schedule. This paper describes the sensitivity to gemcitabine of human head and neck squamous cell carcinoma, ovarian carcinoma, and soft tissue sarcoma, all growing as xenografts in athymic nude mice. The drug was injected i.p. in various schedules at equitoxic, max. tolerated doses, resulting in a reversible wt. loss of 5-15%. Generally, treatment with 120 mg gemcitabine/kg, injected 4 times at 3-day intervals, was more effective than the schedules of daily (5 times 2.5-3.5 mg/kg) or weekly (2 times 240 mg/kg) injections. This 3-day-interval schedule has been previously shown to be active on human pancreas and lung carcinoma xenografts. Addnl. expts. were performed on normal mice bearing the colon 26-10 murine colon carcinoma. The effect of a continuous i.v. infusion system was investigated by giving 2 infusions of 15 mg gemcitabine/kg for 24 h at a 7-day interval. The efficacy of treatment increased dramatically with this infusion schedule, producing complete remissions in most tumors. The data on the effect of gemcitabine in animal tumor models indicate that: (1) the time interval between push injections is important when intermittent schedules are used; (2) continuous infusions over a 24-h period can be very effective in in vivo models.

Answer 66:

Bibliographic Information

Acquired resistance and cross-resistance of gemcitabine to cisplatin or vindesine in human lung cancer xenografted in nude mice. Fujita, Fumiko; Fujita, Masako; Fujita, Masahide; Sakamoto, Yasuo. Experimental Cancer Chemotherapy Res. Lab. Co., Ltd., Japan. Gan to Kagaku Ryoho (1994), 21(16), 2749-55. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 122:95983 AN 1995:313513 CAPLUS

Abstract

One of the problems in the treatment of cancer is the development of resistance to anti-tumor agents when used repeatedly. We described the induction of resistance and cross-resistance to cisplatin (CDDP) or vindesine (VDS) and the side effects of gemcitabine, a new Ara-C deriv., in human lung cancers, Mqnu-1 or H-74 xenografted in nude mice. We investigated the effects of 4-wk treatment with gemcitabine, CDDP or VDS, followed by repeated or alternate therapy after a 4-wk observation period. Gemcitabine was effective and did not show the acquired resistance when given repeatedly. In contrast, CDDP but not VDS, when given repeatedly, showed a decrease of the anti-tumor effect in the second course. Gemcitabine was still effective to the large tumor grown after CDDP or VDS therapy. Thus, gemcitabine may not develop resistance nor show cross-resistance to CDDP or VDS. In addn., repeated treatment with gemcitabine was much safer than CDDP or VDS. These results suggest that gemcitabine is a candidate for the first choice drug in cancer treatment.

Answer 67:

Bibliographic Information

Antitumor activity of combination treatment combining gemcitabine with cisplatin or vindesine against human lung cancer xenografted in nude mice. Fujita, Fumiko; Fujita, Masako; Fujita, Masahide; Sakamoto, Yasuo. Exp. Cancer Chemother. Res. Lab. Co., Ltd., Japan. Gan to Kagaku Ryoho (1994), 21(15), 2595-601. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 122:71529 AN 1995:303437 CAPLUS

Abstract

Gemcitabine is a new ara-C deriv. with much more potent cytotoxic action than ara-C, which may be explained by the fact that its intracellular concn. can be maintained over a long period. We investigated the antitumor activity of combination of gemcitabine with cisplatin (CDDP) or vindesine (VDS) in lung cancer line H-74 that was relatively insensitive to gemcitabine. Mice were obsd. for 8 wk, including the 4 wk treatment period and the subsequent 4 wk drug-free period. The tumor growth inhibition rate, histol. changes, and side effects were evaluated at 4 and 8 wk after the initiation of therapy. The anti-tumor effects of treatment combining gemcitabine with CDDP or VDS were more potent and lasted longer than each drug sep. Statistical anal. shows that the treatment combining gemcitabine with CDDP was additive or synergistic at 4 and 8 wk after initiation, whereas the treatment combining gemcitabine with VDS was only additive at 4 wk after initiation and additive or synergistic at 8 wk after initiation. The side effects of both combination groups were less than those obsd. ni only CDDP or VDS-treatment animals. These results suggest the usefulness of a combination therapy combining gemcitabine with CDDP or VDS in future clin. applications.

Answer 68:

Bibliographic Information

Antitumor activity of LY 188011, a new deoxycytidine analog, against human cancers xenografted into nude mice. Fujita, Masahide; Fujita, Fumiko; Inaba, Hiizu; Taguchi, Tetsuo. Research Institute Microbial Diseases, Osaka University, Japan. Gan to Kagaku Ryoho (1994), 21(4), 517-23. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 121:221179 AN 1994:621179 CAPLUS

Abstract

LY 188011 (gemcitabine) was evaluated for its antitumor effect in 15 human tumors xenografted in nude mice (7 gastric, 2 colorectal, 2 breast, 2 lung and 2 liver cancer lines); in the latter 4 cases, the results were compared with those obtained with mitomycin C. LY 188011 reduced the vol. of tumor xenografts in 7 lines, including drug-resistant colorectal and lung cancer lines. The antitumor effect of LY 188011 was further confirmed by pathol. observation. Moreover, LY 188011 was more potent in 2 lung cancer models than mitomycin C, and it induced fewer side effects. LY 188011 seemed to be an excellent candidate for clin. trials for the treatment of cancer.

Answer 69:

Bibliographic Information

The influence of the schedule and the dose of gemcitabine on the antitumor efficacy in experimental human cancer. Boven, E.; Schipper, H.; Erkelens, C. A. M.; Hatty, S. A.; Pinedo, H. M. Dep. Med. Oncol., Free Univ. Hosp., Amsterdam, Neth. British Journal of Cancer (1993), 68(1), 52-6. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 120:45325 AN 1994:45325 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The therapeutic efficacy of gemcitabine, a new nucleoside analog, was assessed in well-established human soft tissue sarcoma and ovarian cancer xenografts grown s.c. in nude mice. Tumor lines selected had different histol. subtypes, growth rates and sensitivities to conventional cytostatic agents. The 3 different doses and schedules designed from a mean wt. loss between 5% and 15% were i.p. injections of daily 3.5 mg kg-1 × 4, every 3 days 120 mg kg-1 × 4, and weekly 240 mg kg-1 × 2, which ultimately resulted in 19%, 10% and 4% toxic deaths, resp. The weekly schedule induced ≥ 50% growth inhibition in 2/4 soft tissue sarcoma and 4/6 ovarian cancer lines, while in 3 ovarian cancer lines ≥ 75% growth inhibition was obtained. The antitumor effects of gemcitabine appeared to be similar or even better than previous data with conventional drugs tested in the same tumor lines. In comparison with the every 3 days schedule, the weekly and the daily schedule were less effective in 5/7 and 3/3 tumor lines ($P < 0.001$), resp. In another expt. in 3 human tumor lines selected for their differential sensitivity to gemcitabine, weekly injections of 240 mg kg-1 × 6 did not result in a increase in the schedule. However, the 240 mg kg-1 weekly × 6 schedule showed superior effects in 23 tumor lines in comparison with the same dose given every 2 wk × 3 ($P < 0.05$). The preclin. activity of gemcitabine suggests that the drug can induce responses in soft tissue sarcoma and ovarian cancer patients. The authors' results further indicate that clin. trials of gemcitabine in solid tumor types should be designed from a schedule rather than a dose dependence.

Answer 70:

Bibliographic Information

Gemcitabine-mediated radiosensitization of human soft tissue sarcoma. Murphy James D; Lucas David R; Somnay Yash R; Hamstra Daniel A; Ray Michael E Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA Translational oncology (2008), 1(1), 50-6. Journal code: 101472619. E-ISSN:1936-5233. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 18607508 AN 2008436862 In-process for MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND/PURPOSE: Local and systemic control of soft tissue sarcoma (STS) remains a clinical challenge, particularly for retroperitoneal, deep truncal, or advanced extremity disease. 2',2'-Difluoro-2'-deoxycytidine (gemcitabine) is a potent radiosensitizer in many tumor types, but it has not been studied in human STS. The purpose of this study was to determine the radiosensitizing potential of gemcitabine in preclinical models of human STS. MATERIALS AND METHODS: The in vitro radiosensitizing activity of gemcitabine was assessed with clonogenic survival assay on three human STS cell lines: SK-LMS-1 (leiomyosarcoma), SW-872 (liposarcoma), and HT-1080 (fibrosarcoma). Cell cycle distribution was determined using dual-channel flow cytometry. The in vivo radiosensitizing activity of gemcitabine was assessed with subcutaneous SK-LMS-1 nude mice xenografts. Tumor-bearing mice were treated with concurrent weekly

gemcitabine and fractionated daily radiotherapy (RT) (2 Gy daily) for 3 weeks (a total dose of 30 Gy). RESULTS: The 50% inhibitory concentration (IC(50)) of gemcitabine for the human STS cell lines ranged from 10 to 1000 nM. Significant in vitro radiosensitization was demonstrated in all three human STS cell lines using gemcitabine concentrations at and below the IC(50). Maximal radiosensitization was associated with accumulation of cells in early S-phase. SK-LMS-1 xenografts displayed significant tumor growth delay with combined gemcitabine and RT compared to either treatment alone. Treatment related toxicity was greatest in the gemcitabine plus RT arm, but remained at an acceptable level. CONCLUSIONS: Gemcitabine is a potent radiosensitizer in preclinical models of human STS. Clinical trials combining gemcitabine and RT in human STS are warranted.

Answer 71:

Bibliographic Information

Radiosensitization by gemcitabine fixed-dose-rate infusion versus bolus injection in a pancreatic cancer model. Morgan Meredith; El Shaikh Mohamed A; Abu-Isa Eyad; Davis Mary A; Lawrence Theodore S Department of Radiation Oncology, University of Michigan, Ann Arbor, MI 48109, USA Translational oncology (2008), 1(1), 44-9. Journal code: 101472619. E-ISSN:1936-5233. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 18607504 AN 2008436858 In-process for MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

It has recently been shown that fixed-dose-rate (gemcitabine) infusion may be superior to bolus gemcitabine in the treatment of metastatic pancreas cancer. We wished to compare the radiosensitizing effects of fixed-dose-rate gemcitabine infusion to standard bolus injection. We measured weight loss and mouse intestinal crypt survival to determine equally toxic concentrations of gemcitabine administered through a 3-hour fixed-dose-rate infusion versus bolus injection in combination with fractionated radiation. To measure the effect of fixed-dose-rate gemcitabine infusion or bolus injection on radiosensitization, we treated mice bearing Panc-1 xenografts with equally toxic concentrations of gemcitabine (100 mg/kg fixed-dose-rate infusion or 500 mg/kg bolus injection) and fractionated radiation and monitored tumor growth. We found that 100 mg/kg gemcitabine through fixed-dose-rate infusion produced the same weight loss and intestinal crypt toxicity as the 500 mg/kg bolus injection. In nude mice bearing Panc-1 xenografts, fixed-dose-rate gemcitabine infusion produced greater radiosensitization than bolus injection with tumor doubling times of 44 +/- 5 versus 29 +/- 3 days, respectively (*P < .05). Fixed-dose-rate gemcitabine infusion produced enhanced radiosensitization without additional normal tissue toxicity compared to bolus gemcitabine injection. These data support an ongoing clinical trial using fixed-dose-rate gemcitabine infusion combined with conformal radiation in the treatment of locally advanced pancreatic cancer.

Answer 72:

Bibliographic Information

Preclinical in vivo activity of a combination gemcitabine/liposomal doxorubicin against cisplatin-resistant human ovarian cancer (A2780/CDDP). Gallo D; Fruscella E; Ferlini C; Apollonio P; Mancuso S; Scambia G Department of Obstetrics and Gynaecology, Catholic University of the Sacred Heart, Largo A. Gemelli 8, 00168 Rome, Italy International journal of gynecological cancer : official journal of the International Gynecological Cancer Society (2006), 16(1), 222-30. Journal code: 9111626. ISSN:1048-891X. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16445637 AN 2006061953 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Both gemcitabine and liposomal doxorubicin are antineoplastic drugs with clinical activity in platinum-refractory ovarian cancer. The purpose of this study was to evaluate the antitumor activity of a combination gemcitabine/liposomal

doxorubicin administered to athymic mice bearing cisplatin-resistant human ovarian cancer (A2780/CDDP) xenografts. Emphasis was on the use of very low doses of each drug and of different dosing schedules. Data obtained showed that combined treatment with 80 mg/kg gemcitabine and 15 mg/kg liposomal doxorubicin produced a significant enhancement of antitumor activity compared with monotherapy at the same doses of these agents. Noteworthy is the fact that the majority of xenograft-bearing animals receiving the combination therapy demonstrated a complete tumor regression at the end of the study. A similar trend was observed when doses of both drugs were reduced to 20 mg/kg gemcitabine and to 6 mg/kg liposomal doxorubicin. Again, three out of ten mice receiving the combination were tumor free at the end of the study. No significant differences were observed in antitumor activity when comparing the simultaneous vs the consecutive dosing schedule. Remarkably, no additive toxicity was observed in any experimental trials. These data encourage clinical trials to prove the advantages of this combination treatment with respect to the single-agent chemotherapy in platinum-refractory ovarian cancer patients.

Answer 73:

Bibliographic Information

Enhanced efficacy of gemcitabine in combination with anti-CD20 monoclonal antibody against CD20+ non-Hodgkin's lymphoma cell lines in vitro and in scid mice. Smith Mitchell R; Joshi Indira; Jin Fang; Obasaju Coleman Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA 19111, USA. m_smith@fccc.edu BMC cancer (2005), 5 103. Journal code: 100967800. E-ISSN:1471-2407. (IN VITRO); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 16109167 AN 2005491478 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Despite exciting new targeted therapeutics against non-Hodgkin's lymphoma (NHL), chemotherapy remains a cornerstone of therapy. While purine nucleoside analogs have significant activity in low grade NHL, the pyrimidine nucleoside analog gemcitabine has been less extensively studied, but has important activity. Use of the anti-CD20 monoclonal antibody rituximab in combination with chemotherapy for B-NHL is becoming prevalent in clinical practice, but has not been extensively studied in pre-clinical models. METHODS: We have tested the activity of gemcitabine +/- rituximab in vitro and in scid/human NHL xenograft models. We used two t(14;18)+, CD20+ follicular B cell NHL cell lines, DoHH2 a transformed NHL line and WSU-FSCCL isolated from pleural fluid of a patient with indolent NHL. RESULTS: Gemcitabine is cytotoxic to DoHH2 and WSU-FSCCL cells in vitro, and the IC50 is 2-3 fold lower in the presence of rituximab. Apoptosis is also enhanced in the presence of rituximab. Clearance of NHL cells from ascites in scid mice is prolonged by the combination, as compared with either agent alone. Most importantly, survival of scid mice bearing human NHL cells is significantly prolonged by the combination of gemcitabine + rituximab. CONCLUSION: Based on our pre-clinical data showing prolonged survival of mice bearing human lymphoma cell line xenografts after treatment with gemcitabine + anti-CD20 antibody, this combination, expected to have non-overlapping toxicity profiles, should be explored in clinical trials.

Answer 74:

Bibliographic Information

Resistance to gemcitabine in a human follicular lymphoma cell line is due to partial deletion of the deoxycytidine kinase gene. Galmarini Carlos Maria; Clarke Marilyn L; Jordheim Lars; Santos Cheryl L; Cros Emeline; Mackey John R; Dumontet Charles INSERM 590 - Laboratoire de Cytologie Analytique, Faculte de Medecine Rockefeller, Universite Claude Bernard Lyon 1, Lyon, France. fgalma@rockefeller.univ-lyon1.fr BMC pharmacology (2004), 4 8. Journal code: 100967806. E-ISSN:1471-2210. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 15157282 AN 2004302161 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Gemcitabine is an analogue of deoxycytidine with activity against several solid tumors. In order to elucidate the mechanisms by which tumor cells become resistant to gemcitabine, we developed the resistant subline RL-G from the human follicular lymphoma cell line RL-7 by prolonged exposure of parental cells to increasing concentrations of gemcitabine. RESULTS: In vitro, the IC50 increased from 0.015 microM in parental RL-7 cells to 25 microM in the resistant variant, RL-G. Xenografts of both cell lines developed in nude mice were treated with repeated injections of gemcitabine. Under conditions of gemcitabine treatment which totally inhibited the development of RL-7 tumors, RL-G derived tumors grew similarly to those of untreated animals, demonstrating the in vivo resistance of RL-G cells to gemcitabine. HPLC experiments showed that RL-G cells accumulated and incorporated less gemcitabine metabolites into DNA and RNA than RL-7 cells. Gemcitabine induced an S-phase arrest in RL-7 cells but not in RL-G cells. Exposure to gemcitabine induced a higher degree of apoptosis in RL-7 than in RL-G cells, with poly-(ADP-ribose) polymerase cleavage in RL-7 cells. No modifications of Bcl-2 nor of Bax expression were observed in RL-7 or RL-G cells exposed to gemcitabine. These alterations were associated with the absence of the deoxycytidine kinase mRNA expression observed by quantitative RT-PCR in RL-G cells. PCR amplification of desoxycytidine kinase gene exons showed a partial deletion of the dCK gene in RL-G cells. CONCLUSIONS: These results suggest that partial deletion of the dCK gene observed after selection in the presence of gemcitabine is involved with resistance to this agent both in vitro and in vivo.

Answer 75:

Bibliographic Information

Clonal preservation of human pancreatic cell line derived from primary pancreatic adenocarcinoma.
Mohammad R M; Li Y; Mohamed A N; Pettit G R; Adsay V; Vaitkevicius V K; Al-Katib A M; Sarkar F H Department of Internal Medicine, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, Michigan, USA
Pancreas (1999), 19(4), 353-61. Journal code: 8608542. ISSN:0885-3177. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 10547195 AN 2000012686 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Adenocarcinoma of the pancreas generally remains an incurable disease by available treatment modalities, demanding the development of a suitable cell-culture/animal model and the discovery and evaluation of novel therapeutic agents. We report the clonal preservation of a human pancreatic cell line (KCI-MOH1) established from a 74-year-old African-American man diagnosed with pancreatic cancer. Initially the human primary tumor was grown as a xenograft in SCID mice and, subsequently, a cell line was established from tumors grown as a xenograft as reported in our earlier publication. The molecular characterization of the primary tumor, the tumors grown as xenograft, and the cell line all revealed similar genotypic properties. By using an automated DNA sequencer, a K-ras mutation (codon 12, GGT to CGT, Gly to Arg) was detected in the pancreatic tumor tissue taken from the patient, whereas no p53 mutation was detected. The same K-ras mutation and unaltered p53 was also found in the xenograft tumor and in the KCI-MOH1 cell line. Chromosome analysis of the cultured cells revealed: 42,XY,add(3)(p11.2),der(7)t(7;12) (p22;q12),-10,-12,add (14)(p11),-18,add (20)(q13),-22/84, idemx2, which is the same chromosome complement found in xenograft tumors. The KCI-MOH1 cell line grows well in tissue culture and forms tumors in the SCID mice when implanted subcutaneously, as well as in orthotopic sites. The KCI-MOH1 cell line-derived SCID mouse xenograft model was used for efficacy evaluation of bryostatin 1, auristatin-PE, spongistatin 1, and gemcitabine alone and in combination. Tumor growth inhibition (T/C expressed as percentage), tumor growth delay (T - C), and log 10 kill for these agents were 38%, 22 days, and 0.53; 15%, 30 days, and 0.80; 24%, 25 days, and 0.66; and 10%, 33 days, and 0.90, respectively. When given in combination, two of seven gemcitabine + auristatin-PE-treated animals were free of tumors for 150 days and were considered cured.

Animals treated with a combination of bryostatin 1 and gemcitabine and a combination of spongistatin and gemcitabine produced remissions in only one of seven mice. From these results, we conclude that (a) this is the first study illustrating that clonal characteristics of primary pancreatic tumors remained unchanged when implanted in mice and as a

permanent cell line grown in vitro; and (b) there is a synergistic effect between gemcitabine and selected marine products tested in this study, which is more apparent in the gemcitabine and auristatin-PE combination. The results of this preliminary study suggest that these agents should be explored clinically in the treatment of pancreatic cancer.

Answer 76:

Bibliographic Information

Establishment of a human pancreatic tumor xenograft model: potential application for preclinical evaluation of novel therapeutic agents. Mohammad R M; Dugan M C; Mohamed A N; Almatchy V P; Flake T M; Dergham S T; Shields A F; Al-Katib A A; Vaitkevicius V K; Sarkar F H Department of Internal Medicine, Wayne State University School of Medicine, Karmanos Cancer Institute, Detroit, Michigan 48201, USA Pancreas (1998), 16(1), 19-25. Journal code: 8608542. ISSN:0885-3177. (CASE REPORTS); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 9436858 AN 1998097358 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Adenocarcinoma of the pancreas is currently the fifth leading cause of death in the United States. It remains generally incurable by available treatment modalities. We report here on the characterization of a permanent pancreatic cell line (KCI-MOH1), established as a xenograft in severe combined immune deficient (SCID) mice, from a 74 year-old African American male patient diagnosed with pancreatic cancer. Sections from paraffin-embedded tumors excised from SCID mice revealed typical adenocarcinoma of the pancreas. Karyotypic analysis of cultured cells derived from tumors grown in SCID mice revealed a male karyotype with multiple clonal aberrations: 42, XY, add (3)(p11.2), der(7) t(7;12) (p22;q12), -10, -12, add (14)(p11), -18, add (20)(q13)-22/84, idemx2. Immunostaining of KCI-MOH1 tissues shows strong expression of p53 and p21 proteins. The xenograft model was established by transplanting the KCI-MOH1 cells subcutaneously (s.c.) in SCID mice. When the s.c. tumor was transplanted in vivo to other SCID mice, the success rate was 100%, with a doubling time of 8.5 days. The SCID mouse xenograft model was used to test the efficacy of selected standard chemotherapeutic drugs (taxol, gemcitabine, 5-fluorouracil, and Ara-C) and novel biological agents (Bryostatin 1 and Auristatin-PE). Results show that gemcitabine, Ara-C, and Bryostatin 1 were active against KCI-MOH1. The xenograft described herein can be used as an animal model to facilitate the development of novel therapeutic agents against human pancreatic cancers.

Answer 77:

Bibliographic Information

Schedule-dependent therapeutic efficacy of the combination of gemcitabine and cisplatin in head and neck cancer xenografts. Braakhuis B J; Ruiz van Haperen V W; Welters M J; Peters G J Department of Otorhinolaryngology/Head and Neck Surgery, Free University Hospital, Amsterdam, Netherlands European journal of cancer (Oxford, England : 1990) (1995), 31A(13-14), 2335-40. Journal code: 9005373. ISSN:0959-8049. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 8652266 AN 96262876 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Gemcitabine and cisplatin are both drugs with proven clinical activity in various tumour types, have no overlapping toxic side-effects and are different with respect to cellular metabolism. We, therefore, performed an in vivo study to determine the efficacy of the combination of these two drugs using two human head and neck squamous cell carcinoma xenograft lines, subcutaneously growing in athymic nude mice. 100 mg/kg gemcitabine was given intraperitoneally on days 0, 3, 6 and 9 and 4 mg/kg cisplatin intravenously on days 0 and 6. In one tumour line, the combination treatment resulted in better effects than those observed when the drugs were administered individually. In the other cell line,

addition of cisplatin did not increase the moderate effect of gemcitabine. Experiments with single dose injections of both drugs showed adverse effects when the interval was extended to 24 h. These data are of potential interest for clinical application, and suggest that the drugs should be administered either simultaneously or with a short time interval in which cisplatin should precede gemcitabine.